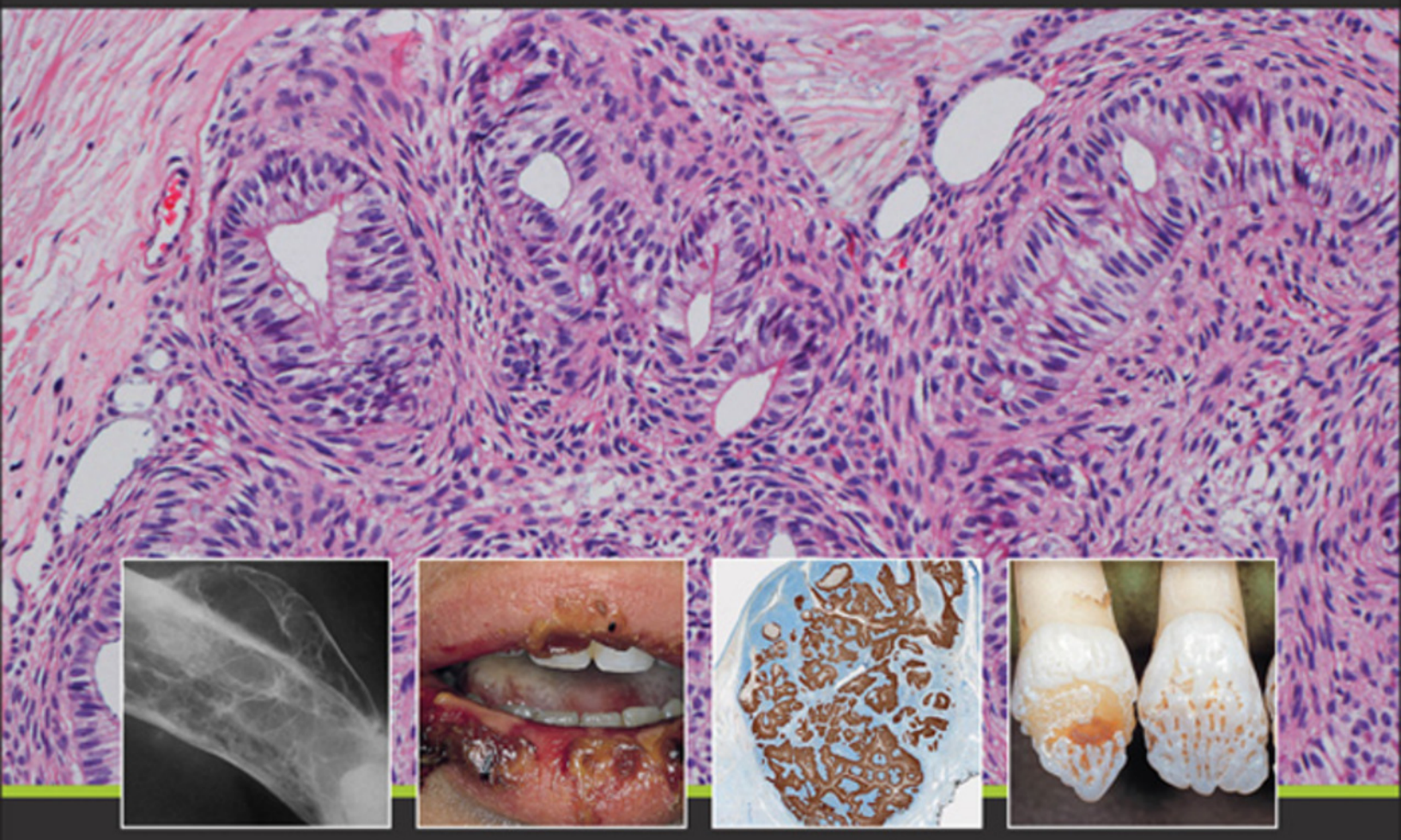
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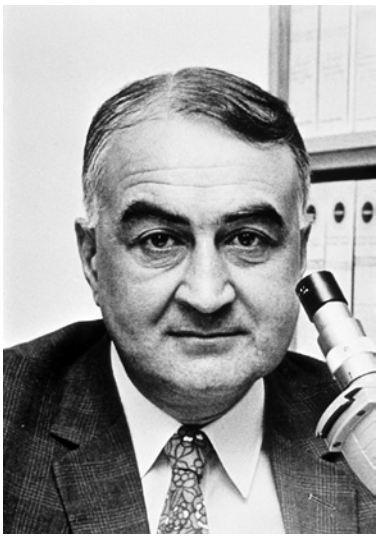
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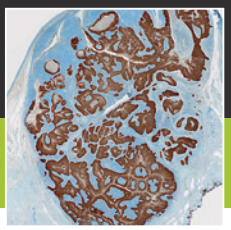
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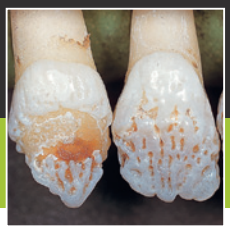
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Cawson's Essentials of Oral Pathology *and* Oral Medicine





E.W. Odell

FDSRCS MSc PhD FRCPath

Professor of Oral Pathology and Medicine,
King's College London
Honorary Consultant in Oral Pathology,
Guy's and St Thomas' NHS
Foundation Trust, London

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Preface

It is interesting to see how this book has evolved over the last 50 years or more. The first edition was the first book to integrate oral medicine, pathology and surgery in a practical, student-orientated fashion. It was truly a book of essentials and was correspondingly small and concise. However, like all textbooks it has grown, fulfilling different functions from those originally envisaged.

The world into which this edition will be launched is very different from that of the last. The ready availability of information on the Internet, changing needs of students and innovative dental curricula have all had an impact. Though this edition contains more facts, its larger size is accounted for by considerably more explanation than previously included. This is intended to meet the higher-level understanding and application of knowledge required of students today.

The demise of the textbook has been long predicted, ever since the Internet was launched. My work on this edition reinforces my belief that the textbook accomplishes something the Internet is incapable of providing. In completely revising this text I have searched the Internet using the standard search engines and open access sources. I have been more than disappointed. Although a few sources provide accurate and up to date information, the majority of easily found Internet resources provide the opposite. Search engine results frequently offer websites with plagiarised and out of date information, fake and predatory open access journals with material that has not been properly peer reviewed, and images of misdiagnosed diseases. The textbook provides a repository of information that is subject to the author's professional scrutiny and comes with context and explanation. There is no comparison.

I hope students will like my attempt to provide more accessible sources to read up on the diseases that interest them. Lists of further reading have been dropped; I doubt they were much used, if at all. There are now PubMed ID references and websites provided where they are immediately relevant. Putting these numbers directly into a search engine will take the reader directly to a selected information source, from where further references can be trusted.

My thanks are due to Veronika Watkins, Alison Taylor, Clive Hewat, Christian Bilbow, and all the team at Elsevier for maintaining the excellent production standards of previous editions.

Producing a new edition such as this takes many hundreds of hours of intensive work, and I am grateful to my colleagues at work for their forbearance but most of all to my wonderful wife Wendy who has supported me unconditionally and maintained her sense of humour during the many months I spent in front of my computer.

E.W.O.
London 2017

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References

References to further reading are now inserted throughout, immediately adjacent to the relevant text. To make searching for web URLs straightforward, links to the relevant websites can be found at http://sites.elsevier.com/cawsonsessentials. Various types of reference are provided, all designed to be immediately available through the internet. In the electronic version of this book they are direct links:

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Principles of investigation, diagnosis and treatment

1

The principles of patient investigation and diagnosis are summarised in Box 1.1.

TAKING A HISTORY

Taking a history and making a diagnosis are not completely generic skills that can be learned and then applied to any patient. Skills of gaining rapport, listening and questioning are always applicable, but to ask targeted incisive questions requires knowledge of disease. Effective history-taking and diagnosis of medical conditions are therefore founded in pathological knowledge.

Rapport is critical for eliciting useful information, and gaining rapport must take into account that almost all patients are nervous to a degree, some are inarticulate, and others are confused. History-taking needs to be tailored to the individual patient.

Initial questions should allow patients to speak at some length and to gain confidence. It is usually best to start with an 'open' question (Tables 1.1 and 1.2). Medical jargon should be avoided, because even regular hospital attenders who appear to understand medical terminology may use it wrongly and misunderstand. When a patient uses technical jargon, it is wise to check what they mean by it. Leading questions, which suggest a particular answer, should be avoided because patients may feel compelled to agree with the clinician.

It is sometimes difficult to avoid interrupting patients when trying to structure the history for the records. Structure can only be given after the patient has had time to give the information. Constant note-taking while patients are speaking is undesirable. Notes should be a summary of relevant information only.

Questioning technique is most critical when eliciting any relevant social or psychological history or dealing with embarrassing medical conditions. It may be appropriate to delay asking such questions until after rapport has been gained. Some patients do not consider medical questions to be the concern of the dentist, and it is important to give reasons for such questions when necessary.

During history-taking, the mental and emotional state of the patient should be assessed. This may have a bearing on some diseases and will also suggest what the patient expects to gain from the consultation and treatment. If the patient's expectations are unreasonable, it is important to try to modify them during the consultation, otherwise no reassurance or treatment may be satisfactory (Box 1.2).

Box 1.1 Principles of investigation and diagnosis

- A detailed medical and dental history
- Clinical examination
 - Extraoral
 - Intraoral
- Investigations selected for specific purposes
 - Testing vitality of teeth
 - Radiography or other imaging techniques
 - Biopsy for histopathology (including immunofluorescence, immunocytochemistry, molecular biological tests)
 - Specimens for microbial culture
 - Haematological or biochemical tests

Table 1.1 Types of questions

Type of question	Example
Open	Tell me about the pain.
Closed	What does the pain feel like?
Leading	Does the pain feel like an electric shock?

Table 1.2 Advantages and disadvantages of types of question

Types of question	Advantages	Disadvantages
Open	Allows patients to use their own words and summarise their view of the problem Allows patients partly to direct the history-taking, gives them confidence and quickly generates rapport	Clinicians must listen carefully and avoid interruptions to extract the relevant information Patients tend to decide what information is relevant
Closed	Elicits specific information quickly Useful to fill gaps in the information given in response to open questions Prevents vague patients from rambling away from the complaint	Patients may infer that the clinician is not really interested in their problem if only closed questions are asked Important information may be lost if not specifically requested Restricts the patient's opportunities to talk

Box 1.2 Essential principles of history-taking

- Introduce yourself and greet the patient by name
- Be culturally aware
- Act courteously and respectfully, maintain professional detachment
- Put patients at their ease, be empathic
- Start with an open question
- Mix open and closed questions
- Avoid leading questions
- Avoid medical and dental jargon and idiomatic expressions
- Listen 'actively'
- Explain the need for specific questions if asked
- Divide the consultation into manageable sections for the patient
- Summarise your findings back to the patient for confirmation of meaning
- Assess the patient's mental state
- Assess the patient's expectations from treatment

Box 1.3 History of the present complaint

- Record the description of the complaint *in the patient's own words*
- Elicit the exact meaning of those words
- Record the duration and the time course of any changes in symptoms or signs
- Include any relevant facts in the patient's medical history
- Note any temporal relationship between them and the present complaint
- Consider any previous treatments and their effectiveness
- Check previous investigations to avoid their unnecessary repetition

Demographic details

The age, gender, ethnic group and occupation of the patient should be noted routinely; even though apparently trivial, such information is occasionally critical. Increasing age predisposes to malignant neoplasms, autoimmune disease tends to have onset in middle-aged female patients and aphthous stomatitis is often diagnosed in the young. Identifying and recording a patient's racial or ethnic group can be misconstrued, but it cannot be avoided for fear of being considered racist. Many diseases have a restricted ethnic distribution that aids diagnosis., such as oral submucous fibrosis or florid cemento-osseous dysplasia.

History of the present complaint

Frequently, a complaint, such as toothache, suggests the diagnosis. In many cases, a detailed history (Box 1.3) is required and sometimes, as in aphthous ulceration, a provisional diagnosis can be made on the history alone.

If earlier treatment has been ineffective, the diagnosis should be reconsidered. Many patients' lives have been shortened by having malignant tumours treated with repeated courses of antibiotics.

Table 1.3 Features required in a pain history

Characteristic	Informative features
Character	Ache, tenderness, dull pain, throbbing, stabbing, electric shock. These terms are of limited use, but information on the constancy of pain is useful
Severity	Mild – responds to mild analgesics (e.g. aspirin/paracetamol) Moderate – unresponsive to mild analgesics Severe – disturbs sleep
Duration	Time since onset. Duration of pain or attacks
Nature	Continuous, periodic or paroxysmal If not continuous, is pain present between attacks?
Initiating factors	Any potential initiating factors Association with dental treatment, or lack of it, is especially important in eliminating dental causes
Exacerbating and relieving factors	Record all and note especially hot and cold sensitivity or pain on eating as they suggest a dental cause
Localisation	The patient should map out the distribution of pain if possible. Is it well or poorly defined? Does it affect an area supplied by a particular nerve or artery? Is the distribution of the pain consistent with anatomy?
Referred pain	Try to determine whether the pain could be referred

Pain is completely subjective and, when physical signs are absent, special care must be taken to detail all its features (Table 1.3). Especially important are features suggesting a dental cause. A fractured tooth or cusp, dental hypersensitivity or pain on occlusion are easily misdiagnosed.

Factors triggering different causes of pain are discussed in detail in Chapter 38.

Medical history

A medical history is important because it aids the diagnosis of oral manifestations of systemic disease. It also ensures that medical conditions and medications that affect dental or surgical treatment are identified.

To ensure that nothing significant is forgotten, a printed questionnaire for patients to complete is valuable and saves time. It also helps to avoid medicolegal problems by providing a written record that the patient's medical background has been considered. Some patients may find it easier to fill in a questionnaire than answer questions. However, a questionnaire alone does not constitute a medical history, and the information must be checked verbally, augmented as necessary and confirmed with the clinician's signature. It is important to assess whether the patient's reading ability and understanding are sufficient to provide valid answers to the questionnaire.

Medical history questionnaires vary widely in style and the questions asked. All dental surgeons should be able to take a history without the guidance of a questionnaire. The questionnaire itself is less important than understanding exactly why the questions are being asked and what follow-up questions are relevant (see Table 1.4). However,

Table 1.4 Questions to be included in a medical history and their relevance*

Question	Subsidiary or follow-up questions	Important features of relevance – not all can be included
Are you taking any medicines, medications or tablets at present?	Including over-the-counter drugs and complementary medicine such as herbal remedies Include medication taken in the past	Potential interactions with treatment for oral conditions Potential oral adverse effects of drugs, of which there are many Steroid use and risk of steroid collapse, infections in immunosuppression Some herbal preparations interact with sedation drugs Patients may forget past courses of drugs with important effects such as bisphosphonates (risk of osteonecrosis), or gold injections (risk of lichenoid reaction) and others
Have you ever been in hospital for any illnesses or operations?	Any problems with the operation or the anaesthetic? … normal recovery, not readmitted, no allergies? How long were you in hospital?	Hospitalisation usually indicates severe health problems; this general question should reveal information on malignant disease, chemotherapy, radiotherapy and immunosuppression Indicates previous reactions to anaesthetics and possibly bleeding problems or other medical complications
Do you carry any medication cards or MedicAlert, Medi-Tag, Mediband or similar devices?		Provide details of medications, doses and effect, usually anticoagulants, steroids, allergies and significant medical conditions Note that some of these alerts may carry patient-reported information as well as medically confirmed information.
Do you have, or have you had, any problems with your heart?	Elicit type, particularly valvular disease	Indicates risk of angina, myocardial infarct or other cardiac emergency in the dental surgery Potential anaesthetic problem Possible predisposition to infective endocarditis, depending on defect
Have you ever had rheumatic fever?	Do you have any heart damage as a result?	Possible predisposition to infective endocarditis
Do you have, or have you had, hepatitis or jaundice?	Known or likely type of hepatitis, if unknown clues may be in where and how it was contracted and the clinical course Questions to exclude non-infectious causes of jaundice such as haemolytic anaemias, gall stones, liver failure, alcohol, etc.	Infection control risk for hepatitis B and C Liver damage can cause coagulation defect, and the metabolic defect can contraindicate prescription of some drugs
Have you ever had epilepsy or other fits or faints?	Assess severity of epilepsy, type of seizure, frequency, duration and eliciting factors Degree of drug control and date and severity of last fit If other type of fits, what cause?	Risk of epileptic attack or status epilepticus in the dental surgery Adverse effects of antiepileptic drugs such as phenytoin Risk of vasovagal attack in dental surgery Fits of unknown cause may relate to head and neck neurological complaints and indicate a CNS cause
Do you have diabetes?	How is it managed? With insulin, other drugs or diet? How well controlled? Ever requiring hospital admission? How is blood glucose monitored? Normal levels and range	Risk of hypoglycaemic collapse in insulin dependent diabetics, and, less likely, hyperglycaemia Diabetes predisposes to infection, particularly candidal but also bacterial and periodontal disease Dry mouth may result from dehydration
Do you have high blood pressure?	Taking the blood pressure may be required and is a recommendation for dentists in some countries. Hypertension is often asymptomatic and dentists have a role in detecting and referring patients with poorly controlled or undetected hypertension.	May indicate risk of stroke, angina or myocardial infarction in the dental surgery Oral adverse reactions of antihypertensive drugs include dry mouth, gingival hyperplasia, lichenoid reactions, burning mouth and taste loss Risk of interaction with some vasoconstrictors in local anaesthetic Anaesthetic risk Patients may faint from hypotension after rising from a supine position for dental treatment
Have you ever been anaemic?	Do you know the reason? Do you or anyone in your family have thalassaemia? For patients of African heritage, do you or anyone in your family have sickle cell anaemia?	Anaemia predisposes to numerous oral conditions including aphthous ulcers, candidosis, glossitis and burning mouth Anaesthetic risk for sickle cell anaemia and thalassaemia Thalassaemia is now so geographically widespread that limiting questioning to those of Mediterranean heritage is too specific

Table 1.4 Questions to be included in a medical history and their relevance* (Continued)

Question	Subsidiary or follow-up questions	Important features of relevance – not all can be included
Do you have any allergies …	Ask specifically about penicillin and other drugs including local anaesthetic	Reveals atopic patients prone to allergy
… to medicines … to metals, foods, plasters, etc. … or asthma, hay fever, rashes, etc.?	Ask whether the patient has ever taken penicillin	Allergies to medication potentially prescribed by the dental surgeon, including related drugs Latex allergy and cross-reacting food allergies Identify potential triggers of attack relevant to dentistry Rashes may be cutaneous counterparts of oral disease Potential adverse effects of steroid inhalers used for asthma
Have you ever had any problems stopping bleeding after a cut or surgery?	Does anyone else in your family have problems with bleeding? Have problems followed tooth extraction? Have you ever taken Warfarin or any medicines to thin your blood?	Risk of haemorrhage following extraction, surgery or possibly local anaesthetic If familial, raises possibility of haemophilia and other inherited bleeding conditions Contraindicates prescription of drugs that prolong bleeding such as aspirin Anticoagulants interact with drugs prescribed for oral conditions and prolong bleeding after surgery
Have you ever come into contact with someone suffering human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)? … or any other sexually transmitted infection?	An open question to allow patients to proffer relevant information in this sensitive area. Not usually followed up unless the patient offers that they are or may be HIV positive, in which case minimum information required is the name of the relevant physician and permission to contact them for details of the condition If positive ask about viral load, CD4 count and medication	Infection control risk following blood exposure Oral manifestations of immunosuppression Risk of significant medical complications that may present to the dental surgeon Oral adverse effects of anti-HIV medication and drug interactions Patients at risk should be encouraged to have an HIV test Gives an indication of degree of immunosuppression and infection risk
Do you smoke? Or use smokeless tobacco or betel quid … … or marijuana, cannabis or other drugs?	Type and amount smoked, expressed in pack years (number of 20-cigarette packs per day multiplied by number of years of smoking). 25 g or 1 oz loose tobacco is equivalent to 50 cigarettes.	Predisposes to oral, nose and sinus and aerodigestive tract carcinoma Predisposes to atheroma, hypertension and cardiac disease Associated with oral red and white lesions and potentially malignant disorders Amenable to cessation advice in the dental setting Cannabis carries additional health risks over smoking, possibly including oral carcinoma
Do you drink alcohol?	Units consumed per week and type of alcohol	Synergistic effect with smoking for oral potentially malignant disorders and oral cancer
For female patients, is there any chance you might be pregnant … … or are trying to become pregnant?	Stage of pregnancy	Risk from X-ray exposure Pregnancy modulates healing and is association with remission in aphthous stomatitis and predisposes to pyogenic granuloma and gingivitis Contraindicates prescription of many drugs
Are you otherwise generally fit and well?		An open question to allow patients to provide information that may not be covered by more specific questions
For parents of child patients – is your child receiving any other therapy or special support?	Type and reason Normal developmental milestones achieved? Any additional support at school?	A broad question to identify behavioural and developmental conditions that may affect provision of treatment
Do any diseases run in your family?		May reveal haemophilia and other bleeding disorders and a host of other genetic diseases and syndromes
Is there anything else about your health you would like to tell me? How is your mental health?		May reveal general malaise, fevers, weight loss, psychiatric problems and reveal attitudes to health and disease not elicited by other questions The stigma attached to mental health and learning difficulty problems requires a subtle approach if this is suspected but nothing has been elicited by previous questioning.

*There is deliberate 'redundancy' in medical history questioning, that is, a point of significance may be covered by questioning from more than one perspective to ensure nothing significant is missed. Thus, even if a patient claims that their heart is fine, rheumatic fever should be asked about specifically and jaundice and hepatitis both explored independently. Patients may well not recognise medical names and react to one question but not another.

This table groups conditions that are related, but some favour following a systems-based approach, a surgical sieve, various mnemonics or a medical history questionnaire. Clinicians should become adept at using whatever system they prefer and use the same system all the time to avoid inadvertent omissions.

some structure is required to ensure no items are missed, and questionnaires perform a useful function in this regard.

If the patient's history suggests, or examination reveals, any condition beyond the scope of the dentist's experience or clinical knowledge, referral for a specialist medical examination may be necessary.

Medical warning cards may indicate that the patient is, for example, a haemophiliac, on long-term corticosteroid therapy or is allergic to penicillin. It is also worthwhile to leave a final section open for patients to supply any other information that they think might be relevant.

A detailed drug history is essential. Drugs can have oral effects or complicate dental management in important ways (Chs 16 & 42).

In the relevant ethnic groups, enquiry should be made about the many potentially carcinogenic habits such as betel quid (pan) or smokeless tobacco use (Ch. 20).

Holistic patient assessment PMID: 24923937

Web URL 1.1 UK GDC standards 4.1.1 URL: https://www.gdc-uk.org/professionals/standards

The dental history

A dental history and examination are obviously essential for the diagnosis of dental pain or to exclude teeth as cause of symptoms in the head and neck region.

Symptoms of toothache are normally recognised as such by patients but are very variable and may masquerade as a variety of conditions from the trivial to the sinister (Box 1.4). The relationship between symptoms and any dental treatment, or lack of it, should be noted.

The family and social history

Whenever a symptom or sign suggests an inherited disorder, such as haemophilia, the family history should be elicited. Ideally, this is recorded as a pedigree diagram noting the proband (presenting case) and all family members for at least three generations. Even when no familial disease is suspected, questions about other family members often lead naturally into questions about home circumstances, relatives and social history which can be revealing if, for example, psychosomatic factors are suspected.

Box 1.4 Toothache and its mimics

- Toothache
 - Pulpitis
 - Periapical periodontitis
 - Fractured cusp/tooth
 - Dentine hypersensitivity
- Mimics of toothache
 - Prodromal herpes zoster
 - Postherpetic neuralgia
 - Trigeminal neuralgia
 - Neuropathic pain after trauma or central nervous system disease
 - Maxillary sinusitis
 - Temporal arteritis
 - Migrainous neuralgia
 - Otitis media
 - Referred pain of angina pectoris
 - Referred pain of temporomandibular joint myofascial pain dysfunction
 - Atypical odontalgia / facial pain

Consent

It is imperative to obtain patients' consent for any procedure, including examination. At the very least, the procedure to be used should be explained to the patient and verbal consent obtained. If no more than this is done, the patients' consent should be noted in their records. However, it is better to obtain written consent, and this is now often required for any minor surgical procedure. Many hospitals now require clinicians to give precise descriptions of treatment plans, however routine, and to obtain written consent. Written treatment plans are also required in dental practice.

Patients have a right to refuse treatment. Any such refusals may sometimes be due to failure of the clinician to explain the need for a particular procedure, or failure to soothe the patient's fears about possible complications. Some of these fears may be irrational, but all fears are real to the patient. In such cases, even prolonged explanations and persuasion may be unsuccessful, and a patient's signature in the notes may then be required as evidence of their wish not to consent.

When a biopsy is necessary, the patient will consent to the surgical procedure but must also be made aware that their tissue will be retained in the pathology department for many years in case future reference to it is needed. When the biopsy is also to be used for DNA analysis, the patient must be made aware of this, and when there are implications for other family members' health, the consent process may be complex.

In the case of more major surgery, a consent form may need to take into account a general anaesthetic, the nature of the operation and significant complications or risks. This will require knowledge of the pathology of the disease. For example, in the case of an ameloblastoma, it would be necessary to point out the risk of recurrence after a conservative removal versus the complications of a larger excision.

For consent to be legally valid, patients must be given sufficient information about the proposed treatment for them to make their own decision and the clinician must check that the information has been understood. This is formalised in the concept of 'informed consent', although being informed is only one factor required to make consent valid under UK law (Table 1.5). The UK law on consent is complex and often enshrined in case law rather than Acts of Parliament. The Mental Capacity Act 2005 and The Human Tissue Act 2004 both govern some aspects, but consent evolves constantly, and readers need to be aware of the regulations and professional advice (the latter often more stringent) in force where they practice. When a written consent is required, a standardised form should be used to ensure compliance with local requirements.

Particular difficulties in oral medicine and surgery arise with the prescription of drugs because reactions are varied but infrequent. Usually, patients do not clearly distinguish risk and harm and tend to make decisions about treatments on the basis of the magnitude of potential harm. It is difficult to explain to a patient that anaphylactic reactions in persons not known to be allergic to penicillin are exceedingly rare but, nevertheless, potentially fatal.

Patients reading the extensive information leaflets provided with prescription drugs are frequently concerned about the risks of even safe drugs such as aspirin. In view of the fact

Table 1.5	Requirements for consent
Capacity	Not impaired for any reason May differ procedure to procedure Understands information given Able to weigh information to make a decision
Voluntary	Given freely Without pressure or undue influence
Informed	Understands nature and purpose of procedure Aware of the operator's training and competence No relevant information is withheld Told of 'material' or 'significant' risks or unavoidable risks, even if small Informed of alternatives to the proposed treatment Aware of the risks of not having the treatment Aware of how any tissue removed will be treated and stored
Clinician	Informed and trained Able to judge capacity
Timing	Consent is a process, not a single event, and must be checked and revisited Consent remains in force until withdrawn Consent should be within a reasonable timeframe of the procedure Material changes in any element must be explained
Recorded	The process of obtaining consent must be recorded Written consent is required for more significant procedures and risks

that it is estimated that 3000 tons of it are consumed every year, the chances of a reaction are almost infinitesimally small. The amount of information to be given to the patient is that which would be expected by 'the prudent patient'. However, patients differ, some reading drug information leaflets avidly, whereas others dispose of them unread. The dentist must balance the information given against the patient's expectation. For surgical interventions the patient must be told all 'material facts', specifically including any dangers of the procedure to that particular patient.

Consent is not normally taken from patients for prescription of medications. However, the same principles apply because significant adverse effects can follow prescription of drugs for dental treatment. It is important to maintain vigilance to reduce risk, for instance by recording allergies and checking before prescribing. Sometimes patients at risk of severe adverse effects can be identified. For example, in the case of azathioprine, patients deficient in the enzyme thiopurine methyltransferase (TPMT) can be excluded from treatment because of their risk of bone marrow toxicity. Unfortunately, such examples are rare, and risks from drugs are unpredictable in type and severity.

It is essential to point out any precautions necessary when taking a particular drug and warn patients to return as soon as they think that there has been an adverse reaction. Adverse reactions should be reported in the UK through the yellow card system.

Web URL 1.2 UK consent: https://www.dentalprotection.org/docs/librariesprovider4/dental-advice-booklets/dental-advice-booklet-consent-uk-excl-scot.pdf?sfvrsn=36

Web URL 1.3 Scotland consent: https://www.dentalprotection.org/docs/librariesprovider4/dental-advice-booklets/consent-(scotland).pdf?sfvrsn=2

CLINICAL EXAMINATION

Extraoral

First, look at the patient, before looking into the patient's mouth. Anaemia, thyroid disease, long-term corticosteroid treatment, parotid swellings or significantly enlarged cervical nodes are just a few conditions that can affect the facial appearance.

Palpate the parotid glands, temporomandibular joints (for clicks, crepitus or deviation), cervical and submandibular lymph nodes and thyroid gland. Lymphadenopathy (Ch. 31) is a common manifestation of infection, but may also signify a malignant disease – the cervical lymph nodes are often the first affected by lymphomas. Note the character (site, shape, size, surface texture and consistency) of any enlargement. Always examine the neck from behind the patient and palpate through slack, not taut, skin. Guide the patient's head forward and to one side with one hand to loosen the skin and platysma muscle and move the sternomastoid muscle, below which some nodes lie. Proper examination of the neck is not possible with the patient supine; the patient should be sitting upright or leaning slightly backward.

Press on the maxilla and frontal bone over the sinuses to elicit tenderness if sinusitis is suspected.

Oral examination

Examination of the oral cavity can only be performed adequately with good light, mirrors and compressed air or other means of drying the teeth. If viscid saliva prevents visualisation of the tissues and teeth, a rinse with a traditional dentists' mouthwash will help. This contains sodium bicarbonate, and the alkaline pH changes the charge on the salivary mucins and makes them more soluble.

Soft tissues

The soft tissues of the mouth should usually be inspected first. Examination should be systematic to include all areas of the mouth. Care should be taken that mirrors or retractors do not obscure lesions. To ensure complete examination of the lateral tongue and posterior floor of mouth, the tongue must be held in gauze and gently reflected from side to side.

Abnormal-looking areas of mucosa should be palpated for scarring or induration indicating previous ulceration, inflammation or malignancy. Examination should include deeper tissues accessible to palpation, including the submandibular glands.

If abnormalities extend close to the gingiva, the gingival crevice or pockets should be probed for any communication. Mucosal nodules, especially those on the gingiva or alveolar mucosa that suggest sinus openings, should be probed to identify any sinus or fistula. Check the openings of the salivary ducts while expressing saliva by gentle pressure. Check that saliva flows freely and equally from all glands and is clear in colour. Do not mistake normal anatomical variations (Table 1.6) for disease.

After examination of the oral mucosa, try to visualise the oropharynx and tonsils.

Retrocuspid papilla PMID: 1065843

Foliate papillae ISBN-13: 978-0723438120

Leukoedema: Review: PMID: 1460680

Table 1.6 Some anatomical variants and normal structures often misdiagnosed as lesions

Structure	Description
Fordyce's spots	Sebaceous glands lying superficially in the mucosa are visible as white or cream coloured spots up to 0.5 mm across. Usually on labial mucosa and buccal mucosa. Occasionally prominent and very numerous (Figs 18.1 and 18.2). Increase in prominence with age
Lingual tonsils	Enlarge with viral infection and occasionally noted by patients. Sometimes large or ectopic and then mistaken for disease (Figs 1.1 and 1.2)
Circumvallate papillae	Readily identifiable but sometimes prominent and misinterpreted by patients or healthcare workers
Retrocuspid papilla	Firm pink nodule 0.5–4 mm diameter on the attached gingiva lingual to the lower canine and lateral incisor, usually bilateral but sometimes unilateral. Prominent in children but regresses with age
Dorsal tongue fur	Furring of the dorsal tongue mucosa is very variable and is heavier when the diet is soft. Even light furring is regarded as pathological by many patients. When pigmented black by bacteria and with overgrowth of the filiform papillae, the condition is called black hairy tongue (Ch. 17)
Leukoedema	A milky white translucent whitening of the oral mucosa which disappears or fades on stretching. Commoner in black African races (Ch. 18)
Tori	Exostoses in the midline of the palate or in the lingual alveolus in the premolar region are termed tori (Ch. 12). They are present by young adulthood and also arise at other sites, particularly on the maxilla over premolar and canine roots.

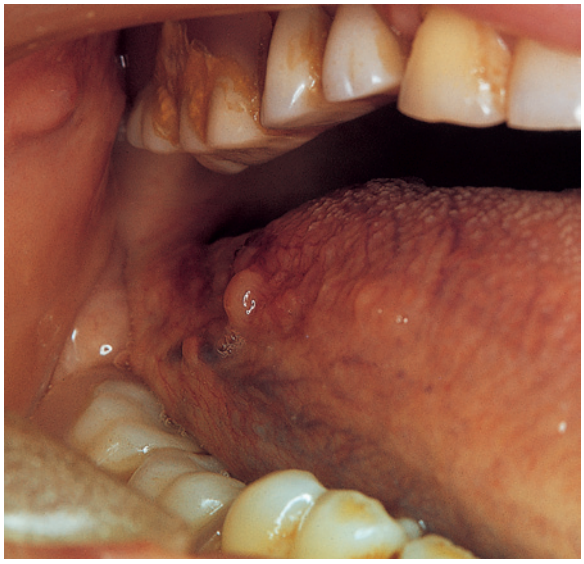


Fig. 1.1 Large foliate papilla or lingual tonsil that may be mistaken for a lesion on the side of the tongue.

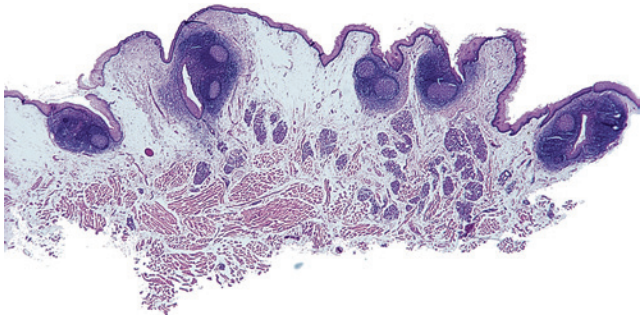


Fig. 1.2 Section showing the nodular surface, small tonsillar crypts and lymphoid follicles in a foliate papilla.

Box 1.5 Precautions for electric pulp testing

- Remember these are sensibility tests of nerve continuity and patient reaction, not direct tests of vitality
- Isolate individual teeth with a small portion of rubber dam if necessary
- No one method is completely reliable; supplement electric methods with hot and cold tests to be certain
- Ensure the correct method is being followed, depending on whether the tester is bipolar or unipolar
- Use an electrically conducting jelly or other agent to ensure good electrical contact
- Always record electric pulp test values in the notes – a progressive change in reading over time may indicate declining vitality
- A definite failure to react or clear vitality are more useful outcomes than the reading on the control
- If results remain uncertain, cut a test cavity or remove suspect restorations without local anaesthetic
- Compare reading with those from control teeth – usually contralateral teeth of the same type
- Use Doppler flowmetry to determine blood flow when pulpal nerve function is compromised, for instance following trauma

Teeth

When undertaking a consultation for a complaint apparently unrelated to teeth, dental examination must still be thorough, both for the patient's sake and for medicolegal reasons. As a minimum, the standing teeth with a summary of their periodontal health, caries and restorative state and any tooth wear should be recorded. When dental pain is a possibility, full charting, assessment of mobility and percussion of teeth are necessary and further investigations will probably be required.

Testing vitality of teeth The vitality of teeth must be checked if they appear to be causing symptoms. It is also essential to determine the vitality of teeth in the region of cysts and other radiolucent lesions in the jaws at presentation. The information may be essential for diagnosis and cannot be determined after treatment.

To be absolutely certain, several methods may have to be used. Checking hot and cold sensitivity and electric pulp testing are relatively easily performed (Box 1.5). Unfortunately, it may not be apparent that a pulp test result is misleading. Care must always be taken to avoid causes of false-positive or false-negative results (Table 1.7). Poorly

Table 1.7 Possible causes of misleading electric pulp test results

Problem	Causes to consider
Pulp by-passed by electric current	Electrical contact with next tooth by touching amalgam restorations or orthodontic appliance Electrical contact with gingival margin by amalgam restoration or saliva film
False positive	Stimulus can be conducted by fluid in necrotic pulp chamber and felt by stimulating nerves in the periodontal ligament
Electrical insulation of the pulp	Large composite or non-conducting restorations
Falsely low reading	Incompletely formed root apex Teeth being moved orthodontically Rubber gloves can partially insulate the electrical circuit of some testers
Partially vital pulps	Multiple canals
No check on validity of results	No normal teeth for comparison
Patient fails to report accurately	Failure to differentiate pulpal from soft tissue or periodontal ligament sensation

localised pulp pain from teeth of dubious vitality can be difficult to ascribe to an individual tooth. In such circumstances, a diagnostic local anaesthetic injection on a suspect tooth may stop the pain and indicate its source.

Pulp test accuracy PMID: 26789282

MEDICAL EXAMINATION

In practice, it is usual for dental investigations to be performed first, but the dentist should be capable of performing simple medical examinations of the head and neck. Examination of the skin of the face, hair, scalp and neck may reveal unexpected foci of infection to account for cervical lymphadenopathy or even malignant neoplasms. The eye can readily be inspected for conjunctivitis or signs of mucous membrane pemphigoid, anaemia or jaundice. Examination of the hands may also reveal relevant information (Table 1.8). Dentists should be able to examine cranial nerve function, but more extensive medical examination by dentists is usually performed only in hospitals.

CLINICAL DIFFERENTIAL DIAGNOSIS

The diagnosis and appropriate treatment may be obvious from the history and examination. More frequently, there are various possible diagnoses, and compiling a differential diagnosis becomes a critical part of the overall diagnostic process. At this stage the clinician has to integrate their knowledge of diseases and their range of presentations with the findings from one specific patient, thinking broadly but keeping focused. If a good differential diagnosis is compiled, then the process of selecting investigations and narrowing down to the final diagnosis will usually be straightforward. Conversely, if the correct diagnosis is not included in the differential diagnosis, it may never be discovered. Mistakes often follow clinicians simply forgetting to consider a possible diagnosis, and a written differential diagnosis helps even experienced clinicians to organise their thoughts.

Table 1.8 Useful diagnostic information from examination of the hands

Site	Signs
Flexor surface of wrist	Rash (or history of rash) consisting of purplish papules suggests lichen planus, especially if itchy
Finger morphology	Clubbing may be associated with some chronic respiratory and cardiac conditions (including infective endocarditis), lung cancer, lung abscesses, cardiac disease and other remote malignancy Joint changes may suggest rheumatoid arthritis (joint swelling, ulnar drift) or osteoarthritis (Heberden's nodes)
Abnormal nails	Koilonychia suggests longstanding anaemia. Hypoplastic nails may be associated with several inherited epithelial disorders of oral significance including ectodermal dysplasia and dyskeratosis congenita
Skin of fingers	May be thin, shiny and white in Raynaud's phenomenon (periodic ischaemia resulting from exposure to cold – often associated with autoimmune conditions particularly systemic sclerosis (Fig. 1.3) or Sjögren's syndrome) Note any tobacco staining. Is the degree commensurate with the patient's reported tobacco use?
Palmar-plantar keratosis	Associated with several syndromes including Papillon–Lefèvre syndrome (including juvenile periodontitis)



Fig. 1.3 Hands with taut, shiny, pale skin on the tapering fingers, a long term effect of Raynaud's phenomenon, in this case associated with systemic sclerosis.

A well-crafted differential diagnosis lists possible diagnoses in order of probability, based on their prevalence and the likelihood of causing a specific combination of symptoms and signs. Even if only one diagnosis seems appropriate, it is worthwhile to note the next most likely possibility and any other causes which can be excluded. This ensures that all appropriate investigations are remembered and reduces the possibility of the patient having to return for further investigations. When the patient's complaint or presentation is relatively non-specific, do not list every possible cause. Too long a list is difficult to convert into a focused investigation strategy, and it may be best to use

generic terms such as 'benign neoplasm' or 'odontogenic tumour' to keep the list manageable.

When the list includes conditions with significant implications for the patient, such as a malignant neoplasm, it is traditional to put them at the top of the list even though their likelihood may be low. This ensures important diagnoses are not forgotten and that they are investigated and excluded first, before moving on to more likely, but less serious, conditions.

INVESTIGATIONS

Innumerable types of investigation are possible. It may be difficult to refrain from asking for every conceivable investigation so as not to miss something unsuspected and to avoid medicolegal complications. Although it may be tempting to explore every possibility, however remote, this approach may prove counterproductive in that it can produce a plethora of reports that confuse rather than inform. The more investigations performed, the more likely one will produce a spurious result.

The differential diagnosis forms the basis on which investigations are selected, and keeping focused on the list ensures that only appropriate investigations are requested. Every investigation must be selected to answer a specific question, and none should be regarded as 'routine tests'.

In all healthcare systems, investigations are expensive, some exceedingly so, and some can only be performed in specialised centres. It is the duty of every clinician to keep the cost-to-benefit ratio of investigations in mind and order only those that will confirm the differential diagnosis or exclude options from it. Often investigations that specifically exclude diseases are the most valuable.

A few diseases, such as mumps, may be diagnosed on the basis of a single test, but others, such as Sjögren's syndrome, may require many tests and some difficult interpretation to make the diagnosis.

Any test will occasionally produce an erroneous result. Sometimes this is the result of inappropriate samples or delay in specimen transport. However, for many blood tests, a result may be flagged as 'out of normal range' because the value is in the highest or lowest 5% of the population. This is not necessarily an abnormal result. Unexpected or inexplicable test results are often best repeated before accepting the result, provided the test is easily performed.

Screening and diagnostic tests

This book is primarily concerned with diagnosis, but the difference between screening and diagnostic tests must be appreciated.

To be useful in diagnosis, a test result, whether positive or negative, must indicate a specific disease or condition. This is measured by the parameters of the sensitivity, specificity, positive predictive value and negative predictive value of the test. The definitions of these parameters are shown in Table 1.9.

Sensitivity describes whether a test can correctly identify a condition, and the specificity determines whether it can correctly exclude a condition. However, no test is completely accurate, and there are always false-positive and false-negative (incorrect) results. You can also see from the definitions that the sensitivity and specificity are only measures that relate to a population in which the correct disease status is already known. That is not helpful when using the test in real life, and the value of the test is better described by the positive and negative predictive values. The ideal test would have a high positive and a high negative predictive value.

Table 1.9 Sensitivity, specificity, positive predictive value and negative predictive value

Parameter	Definition
Sensitivity	The proportion of patients known to have the disease who test positive
Specificity	The proportion of patients known to NOT have the disease who test NEGATIVE
Positive predictive value	The proportion of all positive results that are true positives (correct results)
Negative predictive value	The proportion of all negative results that are true negatives (correct results)

A further complication is introduced by considering the value of tests when they are performed in different circumstances. Suppose a test is not very accurate, but the disease being tested for is very common. Under these circumstances, the test will perform well enough to be useful because a few false-positive results will be outweighed by the value in detecting the many patients with the disease. However, if the disease was very rare, the majority of the results would be false positive and the test would be useless.

The value of the test therefore depends on how it is used. If a clinician performs many tests on all patients, the positive predictive value will not be as high as if the test were used in a more focused manner. This explains why tests must be used to answer specific questions and not thrown randomly at difficult diagnostic dilemmas.

Diagnostic tests are required to have high predictive values, and the more significant the diagnosis, the higher the predictive value must be. Conversely, screening tests are used in population screening and are only intended to identify individuals who might have a disease. Screening tests need to be cheap and easily performed in great numbers, and a lower predictive value is acceptable. Patients who test positive for the screening test will then be referred for more accurate diagnostic tests.

Tests used for diagnosis in oral disease generally have high predictive values. Dentists need to be aware that many less-than-ethical companies sell tests to general dental practitioners for the diagnosis of diseases such as caries, periodontal disease, oral cancer and oral premalignant diseases. It is not always clear whether these are screening or diagnostic tests. In some countries these tests are marketed direct to patients. When evaluating whether using such a test is likely to be effective and its use ethical, it would be strongly advisable to find out what the predictive values of the test would be when used in your own patient population.

Imaging

The most informative imaging techniques in the head and neck are radiography and cone beam computerised tomography (CBCT), medical computerised tomography (CT), magnetic resonance imaging (MRI) and ultrasound. Their advantages and disadvantages are shown in Table 1.10.

Plain radiography is widely available, and simple additional techniques can add value (Box 1.6). Even simple manoeuvres, such as introducing a gutta percha point or probe into a sinus to trace its origins, may provide critical information. It is also advisable to request a formal radiologist's report on radiographic films whenever the radiographic

Table 1.10 Imaging techniques for lesions of the head and neck

Technique	Advantages	Limitations
Conventional radiography	Widely available and inexpensive Simple, many common lesions may be identified with a high degree of accuracy Panoramic radiographs can show unsuspected lesions	Small X-ray dose unavoidable Difficult to interpret in some areas of the jaws because of the complex anatomy Little information about soft tissue lesions
Computerised tomography (CT)	Good definition of soft tissue structures in any plane Useful for areas of complex anatomy such as maxilla or base of skull Definition further improved by use of contrast media	Expensive Available only in hospitals Frightening for patients. Scanner tunnel can provoke claustrophobia Shadows of dental restorations can obscure part of the image Larger X-ray dose than plain radiographs
Cone beam CT	Low-cost high-resolution CT ideal for the head and neck, oral surgery, implantology and endodontics	As CT but lower dose and higher resolution Has quickly become a routine radiological investigation for head and neck diagnosis Image density not directly proportional to bone density Relatively poor soft tissue resolution
Radiography or CT with contrast medium	Valuable for outlining extent of duct systems, hollow structures such as cysts or blood vessels (angiography), etc.	Requires more expertise than plain radiography
Magnetic resonance imaging (MRI)	Produces clear tomograms in any plane without superimposition Particularly good for soft tissue lesions, better than CT No X-ray dose Clear definition of bones and teeth	Expensive and limited availability Frighteningly noisy. May be refused by claustrophobic patient (as for CT) Slow, sometimes over 1 hour Possible risk to the fetus (unconfirmed)
Ultrasound	No X-ray dose Shows soft tissue masses and cysts well Useful for salivary gland cysts, Sjögren's syndrome, stones, and for thyroid and neck lesions May be combined with Doppler flow analysis to measure blood flow through a lesion	Requires expertise in interpretation A dynamic technique interpreted live and difficult to record effectively in pictures Overlying bone obscures soft tissue lesions
Scintigraphy	Uses a radioactive isotope to visualise particular types of cells With technetium 99^{m} provides an assessment of function in each salivary gland Can be used if sialography not possible Other isotopes are used for detection of bone metastases	Equipment not always available Small radiation dose but isotope rapidly cleared
Positron emission tomography (PET scanning)	Short-life radioactive isotope used to identify biochemical activity, usually glycolysis, to identify putative tumour size, location or metastasis Good for identifying unsuspected metastases Helps identify neoplasms when post-surgical artefact or inflammation obscure CT or MRI Also available as a combined PET-CT and PET-MRI scan, but with reduced CT or MRI resolution	Expensive Intake of radioactive substance

features appear unusual or beyond the experience of the clinician.

Imaging and diagnosis ISBN-13: 978-0702045998

Histopathology

Value and limitations

Removal of a biopsy specimen for histopathological examination is the mainstay of diagnosis for diseases of the mucosa, soft tissues and bone. In the few conditions in which a biopsy is not helpful, it may still be valuable to exclude other possible causes.

As with all other investigations, biopsy must address a specific question. For instance, recurrent minor aphthae lack specific microscopic features and biopsy is rarely justified. Conversely, a major aphtha may mimic a carcinoma that only microscopy will exclude.

Histological examination is not a 'test' in the same way as blood investigations. The pathologist will issue a report that describes the macroscopic and histological features seen in the specimen and provide an interpretation, usually specific, sometimes less so (Box 1.7). The interpretation will be based on the clinical information transmitted to the pathologist on the request form, and often this is critical to the reported diagnosis. Pathology reports, and not just the 'bottom line' diagnosis, need to be read and understood because they may contain important caveats about the confidence with which a diagnosis is made or suggestions for further investigations.

Box 1.6 Requirements for useful oral radiographic information

- Always take bitewings when dental pain is suspected. Small carious lesions may be missed in periapical films and poorly localised pain may originate in the opposing arch
- When imaging bony swellings with plain films, always take two views at right angles
- Panoramic tomograms often cannot provide high definition of bony lesions. Only a cross-section of the lesion is in the focal trough, and if the bone is greatly expanded, only a small portion will be in focus. To detect internal structure in bony lesions, plain films such as oblique lateral views of the mandible or oblique occlusal films are better. For better localisation where complex anatomical features are superimposed, cone beam computed tomography may be more useful
- Radiography of soft tissues is occasionally useful, for instance to detect a foreign body or calcification in lymph nodes

Box 1.7 Possible reasons for failures in histological diagnosis

- Specimen poorly fixed or damaged during removal (Figs 1.4 and 1.5)
- Specimen unrepresentative of the lesion or too small
- Plane of histological section does not include critical features
- The disease does not have diagnostic histological features, e.g. aphthous ulcers
- The histological features have several possible causes, e.g. granulomatous inflammation
- The histological features are difficult to interpret, e.g. malignant tumours may be so poorly differentiated that their type cannot be determined
- Inflammation may mask the correct diagnosis

Biopsy

Biopsy is the removal and examination of a part or the whole of a lesion.*

There are several different biopsy techniques (Box 1.8).

The most important technique is surgical biopsy. Leaving aside medical contraindications, the only important contraindications to biopsy are when the site of disease contains important structures, such as the facial nerve in the parotid gland, or when the biopsy risks seeding a tumour more widely in the tissues. The most common parotid neoplasm (pleomorphic adenoma) has an unusual tendency to spread and recur in the incision wound because of its gelatinous nature. In such instances, alternatives would be to perform a fine needle aspiration or excise the entire lesion with a margin of surrounding normal tissue and confirm the suspected diagnosis afterward.

*Biopsy is derived from the Greek words meaning 'to see in life'. Thus, a biopsy specimen is taken from a living patient. Its opposite is necropsy: 'to see in death'; a post-mortem or autopsy.

Box 1.8 Types of biopsy

- Surgical biopsy (incisional or excisional)
 - Fixed specimen for routine diagnosis
 - Frozen sections for rapid diagnosis
 - Fresh tissue for immunofluorescence, microbiological culture or molecular analysis
- Fine needle aspiration biopsy
- Wide needle/core biopsy

Selecting the biopsy site

If the wrong site is selected for biopsy, the chance of a definitive diagnosis is reduced. Choice of site is often a compromise between ease of access, chosen method and removing the ideal tissue.

Identifying the ideal tissue should take precedence and requires the clinician to understand the disease process at a tissue level so that the tissue most likely to show diagnostic features is selected. For large tumours, a central sample is often best, but it is critical to include the margin to assess the growth pattern and possible peripheral invasion. For mucosal disease, ulcers must be avoided because they are inflamed and have no epithelium. For potentially malignant diseases, red and speckled areas are the most important, followed by white areas. For immunobullous disease, the perilesional tissue is best because it is less friable and will not disintegrate on biopsy. However, samples for immunofluorescence should be taken away from the lesion, usually from clinically normal buccal mucosa, because they are used to identify bound autoantibody and not the histopathology of the disease.

It is often stated that a biopsy should include normal tissue at the margin. However, this is widely misunderstood. The pathologist does not require adjacent tissue for comparison; he or she will be very familiar with the normal histological variation in the mouth. However, there may be better reasons for choosing to include normal tissue in the sample. Cancers and some other lesions can be friable and disintegrate on biopsy so that having some normal tissue at one end helps support the sample and holds the suture more firmly. If a malignant process is suspected, the margin is where invasion of surrounding tissue will be seen. When performing an excision biopsy, a small collar of normal tissue may prevent recurrence of some lesions. However, always try to take the largest sample of lesional tissue and only include normal tissue for a specific reason.

Large lesions and those with areas that look or feel different may well require several biopsies to sample them adequately. Those in which the epithelial thickness is markedly increased, such as verrucous carcinoma, may need a sample several millimetres thick to include the underlying connective tissue needed to assess whether or not the carcinoma is invasive.

It can be seen that selecting the correct site can be a challenging intellectual exercise requiring a good differential diagnosis and knowledge of the basic histopathology of the likely disease – just one reason why dental students should know some basic histopathology.

Surgical biopsy methods

This is the surgical removal of tissue to determine the diagnosis before treatment and may be undertaken with a scalpel, biopsy punch, cutting laser, electrocautery or a wide cutting needle ('core biopsy'; Trucut biopsy). In general, a



Fig. 1.4 An artefactual polyp produced by grasping normal mucosa with forceps to steady it during biopsy.

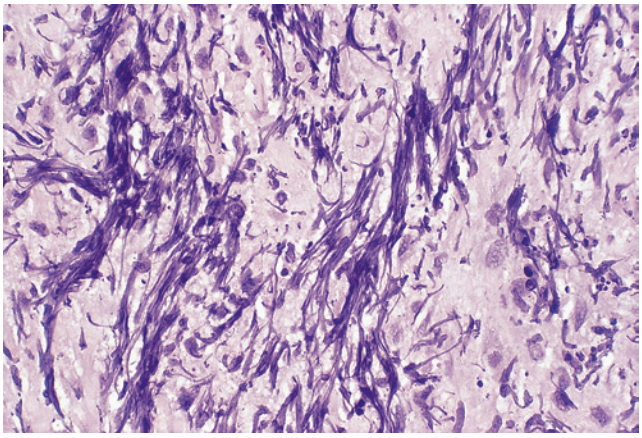


Fig. 1.5 Stringy artefact. This appearance is due to breakage of cells and their nuclei when the specimen is stretched or crushed. It is particularly common in lymphoma and some types of carcinoma.

scalpel biopsy is almost always preferred for intraoral sampling. The tissue is removed cleanly without damage, and the incision can be designed to heal by primary intention. Silk sutures are soft and comfortable in the mouth, and an appointment for removal a few days later provides an opportunity to review healing and discuss the diagnosis. Resorbable sutures may be used to avoid a second appointment but are less comfortable and often persist for many days in the mouth.

Removal of tissue with laser or electrocautery is useful to prevent bleeding, and the coagulated surface requires no sutures. These techniques are most useful to remove excess tissue or excise nodular lesions of the gingiva or mucosa. However, even when properly adjusted, the heat or electrical current will pass through the tissue and denature it, rendering a proportion of the sample unsuitable for diagnosis. Electrocautery is particularly prone to damage epithelium over a wide area and should never be used for a biopsy to assess dysplasia or other epithelial diseases.

Box 1.9 Core or needle biopsy

- Needle up to 2 mm diameter is used to remove a core of tissue
- Specimen processed as for a surgical biopsy
- Larger sample than fine needle aspiration (FNA), preserves tissue architecture in the specimen
- Definitive diagnosis more likely than with FNA
- Risk of seeding some types of neoplasms into the tissues
- Risk of damaging adjacent anatomical structures
- Useful for inaccessible tumours, e.g. in the pharynx or lymph nodes
- Less used in the head and neck now that FNA is more widely available, but may be the next step if FNA fails

Cutting needles or core biopsies are useful to remove a core of tissue, usually 1 mm or so in diameter, from deeper structures such as lymph nodes in the neck (Box 1.9).

A biopsy punch is a circular cutting blade designed to excise a circle of skin. These work well on skin because when the blade penetrates to the subcutaneous fat, a cylinder of skin is mobilised and can be lifted upwards and sliced off. However, punches are badly suited to oral biopsy. The circular blade will only cut taut tissue so that flexible mucosa has to be stretched before cutting. After cutting the sample springs back to its original size, and may then be too small, less than half the punch diameter. The round wound does not lend itself to healing by primary intention or easy closure with sutures. Punch biopsy is often recommended on firm tissue such as the palate and for salivary neoplasms on the palate. At these sites, it is easy to orientate the punch perpendicular to the tissue. Even here it can fail if the deep core of tissue remains fixed to the patient and only a disc of overlying mucosa comes away. Elsewhere a scalpel biopsy is almost always preferred. Despite this, punch biopsy has become popular with dentists because of its speed and simplicity. It is better to take a biopsy with a technique you are happy with than to avoid it, but biopsy punches must be used intelligently.

Surgical biopsy may be incisional or excisional. Incisional biopsy is the removal of part of the lesion for diagnosis only. In excisional biopsy, the whole lesion is removed. The latter is usually performed to confirm a confident clinical diagnosis or when a lesion is too small to require diagnosis and removal in separate steps.

Oral biopsy is a simple procedure that should be within the capability of any dentist. Avoiding or referring for a biopsy in the mistaken belief that the procedure is too unpleasant for general practice is unwarranted. Surveys show that patients rarely complain or suffer adverse consequences from mucosal biopsy, often take no analgesia afterward and much prefer to have their disease properly investigated. Occasionally, general anaesthesia is required for children or problem patients, and referral is necessary. For those that gag, a short-acting benzodiazepine is usually effective.

The pathology request form should contain all the clinical information used to reach the clinical diagnosis. The purpose is to ensure an accurate diagnosis and not (as some clinicians seem to think) to see whether the pathologist can guess it without the relevant information. If appropriate, give the vitality of teeth associated with the lesion.

Box 1.10 Essential biopsy principles

- Choose the most diagnostic or suspicious area, e.g. red area when potential malignancy is suspected
- Avoid ulcers, sloughs or necrotic areas
- Give regional or local anaesthetic – do not inject into the lesion
- Include normal tissue margin if the lesion itself may be friable or malignancy is suspected
- Specimen should preferably be at least 10 x 6 mm and 2 mm deep for mucosal disease, larger for large lesions, smaller on mucoperiosteum
- For mucosal disease, specimen edges should be vertical, not bevelled
- Design the sample shape and incision for easy primary closure
- Before incising, pass a suture through the specimen to control it and prevent it being swallowed or aspirated by the suction
- For large lesions, several areas may need to be sampled
- Include every fragment removed for histological examination
- Never open, incise or divide the specimen, always send it intact
- Suture and control any post-operative bleeding
- Label specimen bottle with patient's name and clinical details
- Warn patient of possible soreness afterward. Give or recommend an analgesic
- Check the histological diagnosis is consistent with the clinical diagnosis and investigations
- Discuss with pathologist or repeat biopsy if diagnosis is unclear or not understood

The essential principles of biopsy are summarised in Box 1.10.

Patient view: PMID: 11235976

Frozen sections

Frozen section technique allows a stained slide to be examined within 10 minutes of taking the specimen (Box 1.11). The tissue is sent fresh to the laboratory to be frozen by immersion in liquid nitrogen (–196°C) or dry ice (–78°C), very cold to ensure freezing is near instantaneous and does not allow time for ice crystals to form in the tissue. A section is then cut on a refrigerated microtome and stained. The equipment for frozen sections is often in the theatre suite to speed the process even further.

Frozen sections can only be justified if the rapidity of the result will make an immediate difference to the operation in progress because the technique is less accurate than routine histopathology. This low risk of misdiagnosis means that frozen section is used more frequently to assess whether excision margins are free of a cancer than to make a primary diagnosis. If a rapid diagnosis is required in other circumstances, techniques such as fine needle aspiration biopsy or a routine specimen with special rapid laboratory processing are usually preferable.

Fine needle aspiration biopsy

Removing very small numbers of cells by aspiration using a fine needle, even if not completely conclusive, is often sufficient to distinguish benign from malignant neoplasms, to initiate treatment or to indicate a need for further investigations. FNA should be used as an early step in the diagnosis of salivary neoplasms, lymph nodes in the neck, thyroid lumps and other deep tissues. Among the diagnoses that can be confidently made on FNA are many types of salivary neoplasm, tuberculosis and high-grade lymphomas (Box 1.12).

Box 1.11 Advantages and limitations of frozen sections

- Can establish, at operation, whether or not a tumour is malignant and whether excision needs to be extended
- Can confirm, at operation, that excision margins are free of tumour
- Appearances differ from those in fixed material
- Freezing artefacts due to poor technique can distort the cellular picture
- Definitive diagnosis sometimes impossible
- Only to be used when the result will alter the immediate surgical plan

Box 1.12 Principles and uses of fine needle aspiration biopsy

- A narrow (21-gauge) needle is inserted into the lesion and cells aspirated and smeared on a slide
- Rapid and usually effective aid to diagnosis of swellings in lymph nodes and parotid tumours especially
- Cells can be fixed, stained and examined within minutes
- Valuable when surgical biopsy could spread tumour cells (e.g. pleomorphic adenomas)
- For deep lesions, ultrasound or radiological guidance may be used to ensure that the needle enters the lesion
- No significant complications
- Small size of the needle avoids damage to vital structures in the head and neck
- Cells may be pelleted and processed for sections to allow immunocytochemistry and other specialised stains
- Some sample may be sent for microbiological culture
- Small specimen may be unrepresentative; several 'needle passes' often taken
- Definitive diagnosis not always possible (though a differential diagnosis may be very helpful to plan treatment)

Brush biopsy and exfoliative cytology

This technique uses a round stiff-bristle brush to collect cells from the surface and subsurface layers of a lesion by vigorous abrasion and is discussed more fully in Chapter 20. It is an excellent method for taking small samples for experimental analysis but has not yet achieved an evidence base for oral diagnosis. The sample removed can be analysed in a variety of ways.

Exfoliative cytology is examination of cells scraped from the surface of a lesion but samples only surface cells and provides no information on deeper layers. It is no longer

Box 1.13 Uses and limitations of brush biopsy

- Quick, easy
- Samples all levels in the epithelium, but no deeper
- Local anaesthetic not required
- Useful research technique
- Value depends on the analytical method applied to the sample
- Unreliable for diagnosing cancer. Frequent false-positive and false-negative results

Box 1.14 Essential points about specimen fixation

- Fixation is a critical step to prevent autolysis and degradation of the microscopic structure of the specimen
- The usual, routine fixative is 10% formal saline (formaldehyde solution in saline or, ideally, in a neutral pH saline buffer)
- Fixation must be complete before the specimen can be processed
- Fixative must diffuse throughout the specimen–fixation is a slow process
- Small surgical specimens fix overnight, but large specimens take 24 hours or longer
- Chemical reaction with the tissue causes the fixative to become weaker as fixation proceeds. Therefore, specimens should generally be put in at least ten times their own volume of fixative
- Never fix specimens for microbiological culture or immunofluorescence; take these fresh to the laboratory immediately on removal or use special transport media

used in the mouth, brush biopsy (Box 1.13) having superseded it.

Laboratory procedures

Although a clinician does not need to understand the details of laboratory procedures, it is necessary to understand the principles to enable the optimal results to be obtained. Failure to prepare or send the specimen appropriately can prevent diagnosis and necessitate an additional biopsy.

Fixation

Fixation is a key process. The surgeon must immerse the specimen in ten times the specimen volume of 10% formal saline immediately on removal. Do not delay. In the absence of proper fixative, it is better to delay the biopsy and obtain the correct solution. Specimens placed in alcohols, saline or other materials commonly available in dental surgeries are frequently useless for diagnosis (Box 1.14). Do not confuse 10% formal saline (formol saline) with normal saline. Formal saline is formaldehyde dissolved in saline and kills and fixes tissue to prevent autolysis. Normal saline is isotonic saline infusion, not a fixative.

Special types of fixative are required for electron microscopy and for urgent specimens. Whenever microbiological culture is required, the specimen should be sent fresh to the laboratory or a separate specimen taken because fixation will kill any micro-organisms.

Table 1.11 Examples of haematoxylin and eosin staining of various tissues

Eosin (acidic, red)	Haematoxylin (basic, blue)
Cytoplasm of most cells*	Nuclei (DNA and RNA)
Keratin	Mucopolysaccharide-rich ground substance
Muscle cytoplasm	Reversal lines in decalcified bone
Bone (decalcified only)	
Collagen	

*The cytoplasm of some cells (such as oncocytes in some salivary gland tumours) is intensely eosinophilic. In others such as plasma cells it is basophilic or intermediate (amphophilic).

Tissue processing

The fixed tissue is dehydrated by immersion in a series of solvents and impregnated with paraffin wax. The wax block is mounted on a slicing machine called a microtome and sections, usually 4 µm thick, are cut and mounted on glass microscope slides for staining. It takes 24–48 hours to fix, process, section and stain a specimen before the pathologist can report on it.

Some common stains used for microscopy

The combination of haematoxylin and eosin (H&E) is the most common routine histological stain. Haematoxylin is a blue-black basic dye; eosin is a red acid dye. Their typical staining patterns are shown in Table 1.11.

Periodic acid–Schiff (PAS) stain is probably the second most frequently used stain. It stains sugar residues in carbohydrates and glycosaminoglycans pink. This is useful to identify salivary and other mucins, glycogen and candidal hyphae in sections. Alcian blue is a turquoise stain for proteoglycans with negatively charged sugars, such as the sialic acid containing salivary mucins. Salivary mucins therefore stain with both PAS and Alcian blue, whereas ground substance in connective tissue stains only with Alcian blue.

Decalcified and ground (undecalcified) sections

Specimens containing bone and teeth need to be softened by decalcifying in acid to enable a thin section to be cut. This delays the diagnosis by days or weeks according to the size of the specimen and technique used.

Decalcification must be avoided if examination of dental enamel is required, for instance to aid diagnosis of amelogenesis imperfecta, because the heavily mineralised enamel is almost completely dissolved away. In such cases, a ground section is prepared by sawing and grinding using special saws and abrasives.

Immunofluorescent and immunohistochemical staining

Immunostaining methods make use of the highly specific binding between antibodies and antigens to stain specific molecules in the tissues.

Antibodies that recognise specific antigens of interest can be purchased. They are produced either by immunising animals with the purified target molecule and then purifying the resulting antibodies from serum, or generated *in vitro* (monoclonal antibodies). The staining process is shown in Figs 1.6–1.8. The antibody binds extremely specifically to the target molecule, and the combination is made visible, either by binding a fluorescent molecule that can be seen in an ultraviolet microscope or an enzyme such as peroxidase that can react with a soluble substrate to form a visible red

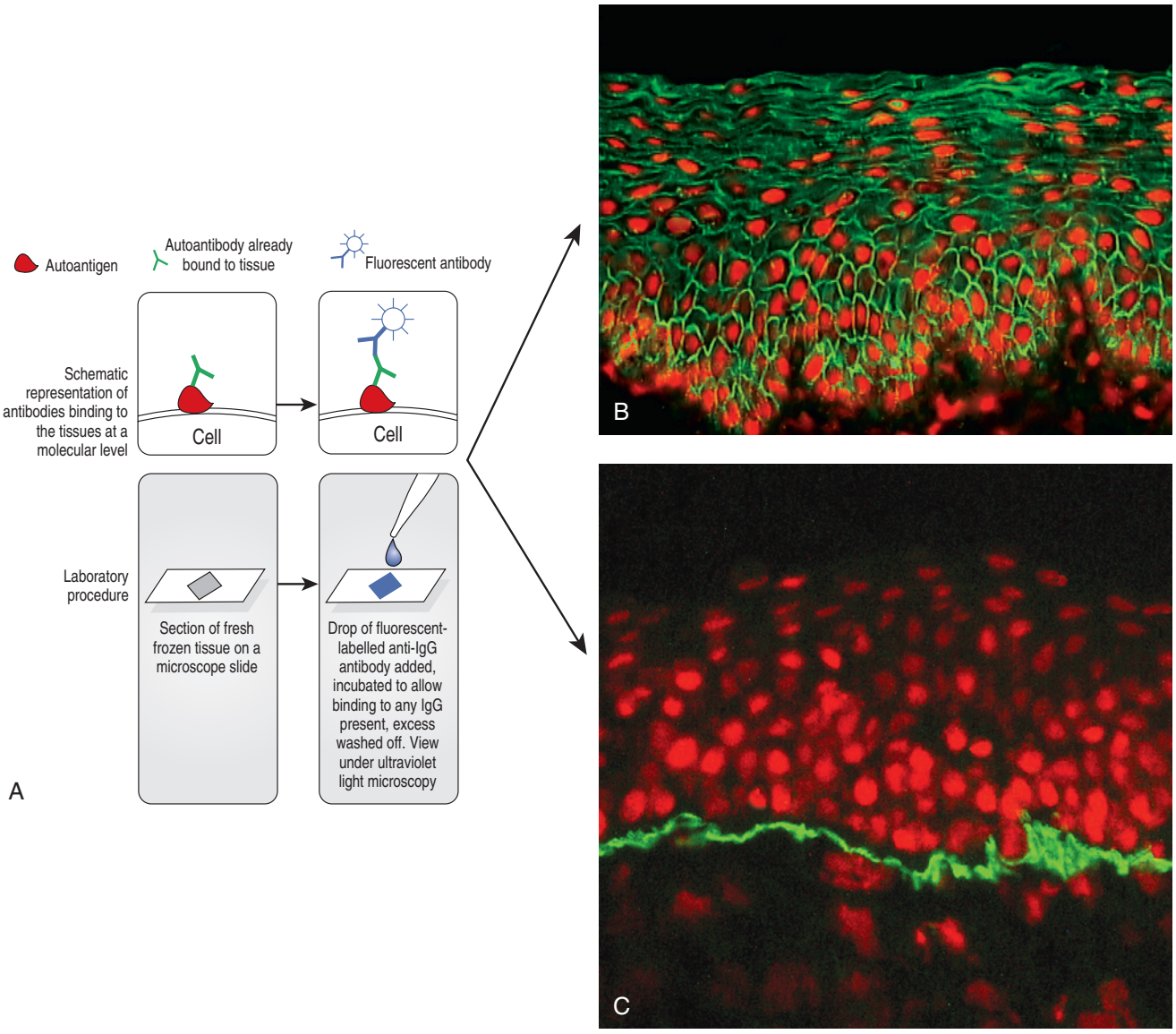


Fig. 1.6 Method and application of direct immunofluorescence. (A) Example: diagnosis of pemphigus and pemphigoid. Aim: to detect the site of the immunoglobulin (IgG) autoantibody already bound to the tissues in a biopsy. Green fluorescence indicates site of antibody binding; red fluorescence is a stain for cell nuclei to make the tissue structure more easily interpreted. (B) In pemphigus, green fluorescence reveals IgG autoantibody bound around the surface of the prickle cells in the epithelium (see Fig. 16.28). (C) In pemphigoid, green fluorescence reveals IgG autoantibody bound along the basement membrane (see Fig. 16.33). *(Images courtesy Dr Balbir Bhogal.)*

or brown deposit. Immunofluorescence is the more sensitive technique.

Immunostaining has revolutionised histological diagnosis. Antibodies are available for immunostaining many cell components and are widely used to identify epithelium (by staining cytokeratin molecules), lymphocyte subtypes (by staining T and B cell membrane antigens), viruses and cell proliferation (by staining molecules involved in the cell cycle). In most laboratories, immunostaining is a relatively cheap automated process.

It is important to know when immunostaining is required because fixation or decalcification may denature the antigens in the tissue and so prevent the antibody binding. Specimens for immunofluorescence must not be fixed in formalin but immediately be sent to the laboratory or sent in special transport medium.

The main circumstances in which diagnosis depends on immunostaining are shown in Table 1.12.

Molecular biological tests

Molecular diagnostic tests have revolutionised medical diagnosis, particularly in screening for and identifying genetic abnormalities and for rapid identification of bacteria and viruses. Techniques are evolving rapidly, and only principles will be illustrated. DNA sequencing and techniques for detecting messenger RNA expression are now rapid and inexpensive, and many medical tests based on single-sequence targets are being replaced by targeted sequencing of multiple specific genes or even whole-genome sequencing.

These methods are not yet widespread in dentistry, but are available in most large hospitals. When confronted with a difficult diagnosis, it is sensible to discuss the case with the pathologist or microbiologist before biopsy, to ensure that appropriate samples are available for these specialised tests.

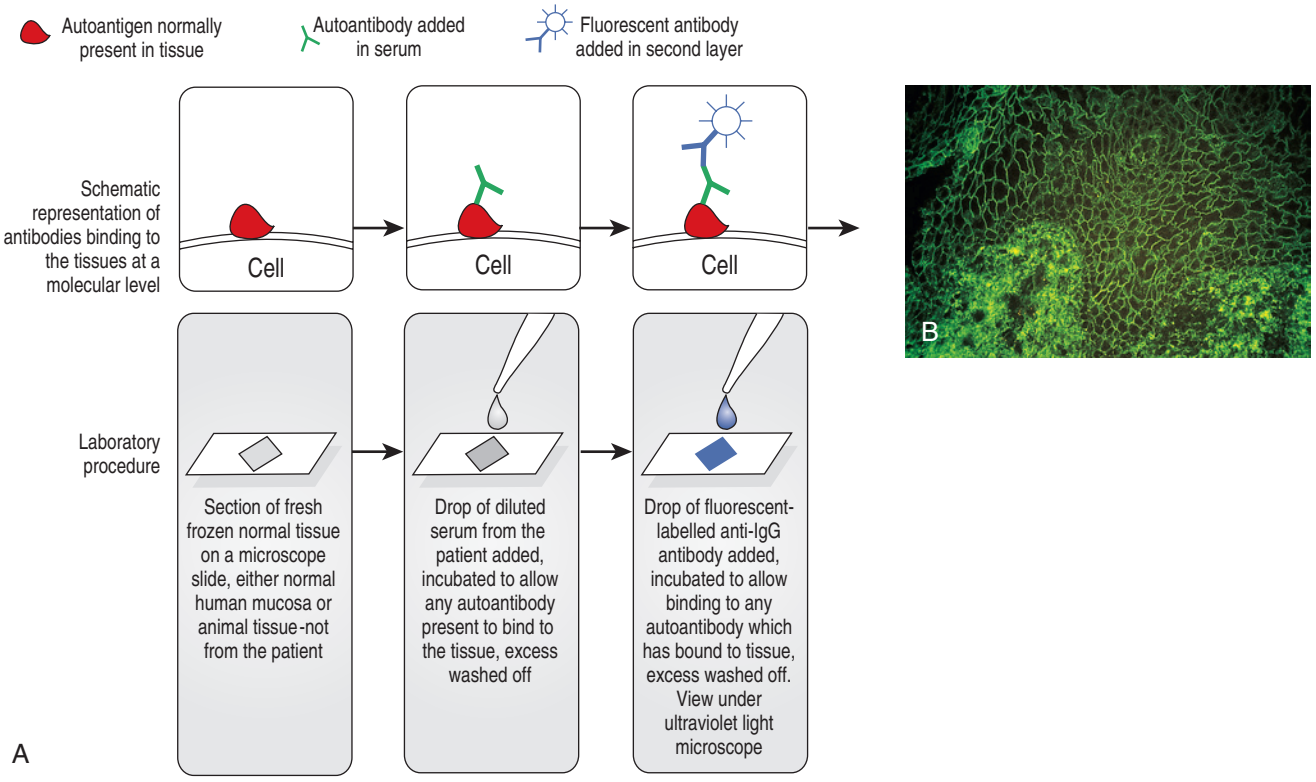


Fig. 1.7 Method and application of indirect immunofluorescence. (A) Example: control of treatment for pemphigus. Aim: to detect circulating autoantibody in the serum of patients with pemphigus. (B) If present, serum autoantibody binds around the surface of the prickle cells in the epithelium and is revealed by the binding to it of the green fluorescent antibody. In this example the nuclei are not counterstained red.

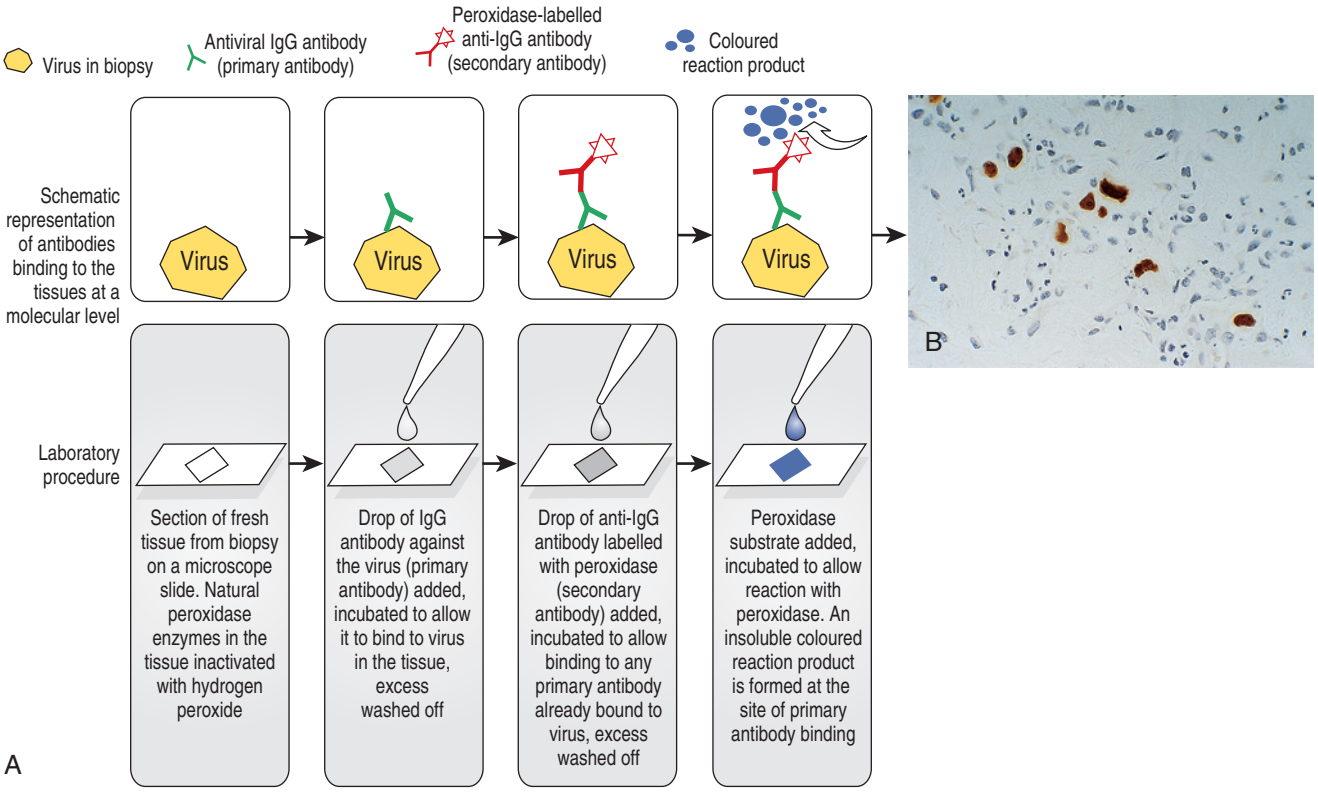


Fig. 1.8 Method and application of immunocytochemistry. (A) Example: diagnosis of viral infection. Aim: to detect viral antigens in infected cells. (B) In this example, brown reaction product identifies cells infected with cytomegalovirus.

Table 1.12 Important uses of immunostaining techniques

Disease	Molecule detected	Significance
Infections	Specific pathogens	Epstein Barr virus in epithelial cells in oral hairy leukoplakia, Treponema pallidum in ulcers indicates syphilis
Pemphigus	Autoantibody bound to epithelial desmosomes (desmoglein 3)	Indicates pemphigus
Pemphigoid	Autoantibody and/or complement C3 bound to basement membrane	Indicates pemphigoid
Myeloma or B-cell lymphoma	Monoclonal production of kappa or lambda light chains of immunoglobulin	Monoclonal production (production of only one isotype of light chain) indicates a neoplastic process. Production of both types indicates a polyclonal infiltrate that is inflammatory in nature
Lymphomas	Cell surface markers specific for different types of T and B cells	Indicates whether a lymphoma is of B- or T-cell origin and its type
Undifferentiated tumours	Intermediate filaments (components of the cytoskeleton)	Presence of cytokeratins indicates an epithelial neoplasm, vimentin a mesenchymal neoplasm and desmin or myogenin a muscle neoplasm

NB Positive reactions, in themselves, are not necessarily diagnostic of disease and must be interpreted in the light of other histological and clinical findings.

Polymerase chain reaction and quantitative polymerase chain reaction analysis

When a known DNA or RNA sequence is associated with a specific disease, it can be detected by polymerase chain reaction (PCR). In this test, the clinical sample is solubilized, and the nucleic acids within it hybridised with probes complementary to the target sequence. If, and only if, the target sequence is present, PCR will copy the nucleic acid repeatedly until enough is synthesised to be detected, either in an electrophoresis gel (Fig. 1.9) or by another laboratory method. PCR is rapid and can be automated on robotic analysers.

Common applications of PCR are detecting pathogens or mutations in genes. Identification of mycobacteria is a good example of the value of this type of test. Previously, identification of mycobacterial infection required approximately 6 weeks to culture the sample. PCR can be performed in 48 hours, is more sensitive and differentiates different types of mycobacteria with a high degree of precision. PCR is also used to detect the causative mutation of fibrous dysplasia and to detect micrometastases in sentinel node biopsy.

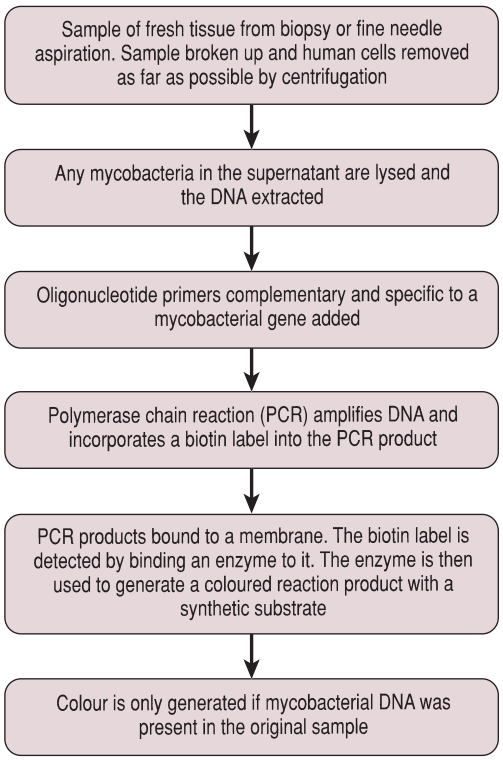


Fig. 1.9 Example application for the technique of polymerase chain reaction for identification of mycobacterial infection.

PCR is extremely sensitive. It can detect a single copy of a sequence in a sample, but this high sensitivity makes it prone to false-positive results. Quantitative PCR (qPCR) is an automated process that detects the PCR product while the amplification is in progress and uses the rate of amplification to measure how many copies of the target sequence were originally present in the sample. This allows threshold values for a true positive result to be defined and adds a further level of confidence in the result.

In situ hybridisation and fluorescent in situ hybridisation analysis

Known DNA and RNA sequences can also be detected by in situ hybridisation (ISH) or fluorescent in situ hybridisation (FISH). As in PCR, the sequence of interest is detected by hybridising with a complementary probe, but the hybridisation is performed on tissue sections instead of on solubilised tissue. As in PCR, the probe will only bind if the target sequence is present. Once bound, the probe can be rendered visible by a fluorescent marker or enzyme reaction in the same way that antibodies are visualised in immunohistochemistry. In situ hybridisation is less sensitive than PCR but has the advantage that the location of the target sequence can be seen in the tissue, so that it can be confirmed it is in the expected place, in the correct tissue, and in the cell nucleus or cytoplasm. This adds an additional level of confidence that the test is detecting the correct target and makes it popular for tumour diagnosis. PCR, being performed on solubilised tissue, cannot demonstrate this.

In situ hybridisation is an automated staining process in many laboratories and often used to detect viruses in tissues. Epstein Barr virus and HPV type 16 genes integrated in

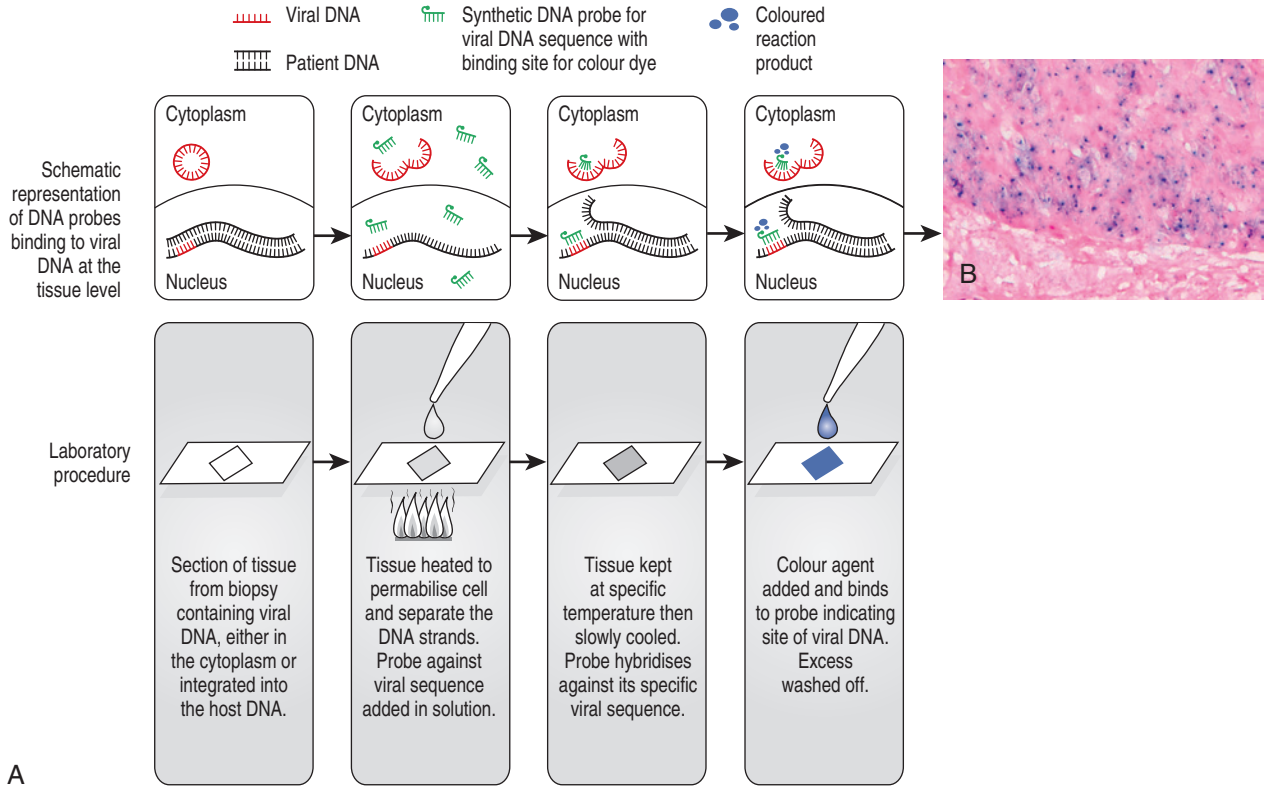


Fig. 1.10 (A) Method and application of in situ hybridisation to detect viral DNA in tissues. (B) In this carcinoma, blue colour reaction product indicates the site of human papillomavirus DNA.

oropharyngeal carcinoma cells are common applications in dentistry.

It is also the method of choice to detect the fusion genes that result from chromosomal translocations, which are often specific to individual types of salivary neoplasms (Ch. 23). The break points in the chromosomes are known, and two probes labelled with different colour fluorescence markers are designed to bind on each side of the break point. In a normal cell the probes bind close together, one on each side of the potential break point, and can be seen down a microscope as four spots of colour in each nucleus (because there are two copies of each gene in a normal cell). Both colours are visible close together. If one of the gene copies is rearranged (the gene is broken), one pair of markers binding to the normal chromosome will show the normal pattern. The fluorescent markers on each side of the broken gene no longer bind close together and are seen as two widely separated spots of colour in the nucleus.

The application of in situ hybridisation is shown in Figs 1.10 and 1.11.

Haematology, clinical chemistry and serology

Blood investigations are clearly essential for the diagnosis of diseases such as leukaemias, myelomas or leukopenias which have oral manifestations, or for defects of haemostasis that can greatly affect management. Blood investigations are also helpful in the diagnosis of other conditions such as some infections and sore tongues or recurrent aphthae that are sometimes associated with anaemia.

As noted earlier, tests should address specific questions (Table 1.13). The request form should always be completed with sufficient clinical detail to allow the haematologist or clinical chemist to check that the appropriate tests have been ordered and to allow the interpretation of the results. It is important to include details of any drug treatment on blood test request forms. Always put the blood into the appropriate tube because some anticoagulants are incompatible with certain tests. A haematologist will not be impressed by a request for assessment of clotting function on a specimen of coagulated blood.

Microbiology

Despite the fact that the most common oral diseases are infective, traditional microbiological culture of organisms is surprisingly rarely of practical diagnostic value in dentistry (Table 1.14, Box 1.15). Direct Gram-stained smears will quickly confirm the diagnosis of thrush or acute ulcerative gingivitis, and H&E-stained smears can show the distorted, virally infected epithelial cells in herpetic infections more easily than microbiological tests for the organisms themselves.

A key microbiological investigation is culture and sensitivity of pus organisms. Whenever pus is obtained from a soft tissue or bone infection, it should be sent for culture and determination of antibiotic sensitivity of the causative microbes. Those of osteomyelitis, cellulitis, acute parotitis or other severe infections need to be identified if appropriate antimicrobial treatment is to be given. However, such treatment has usually to be started empirically without this information; the sensitivity test may dictate a change of treatment.

Soft tissue infections of the head and neck are often treated without microbiological diagnosis. This is partly because the flora is complex and mixed with many anaerobes and organisms that are difficult to culture. The anaerobes do not survive ordinary sample-taking procedures. Culture results are usually a poor reflection of the actual

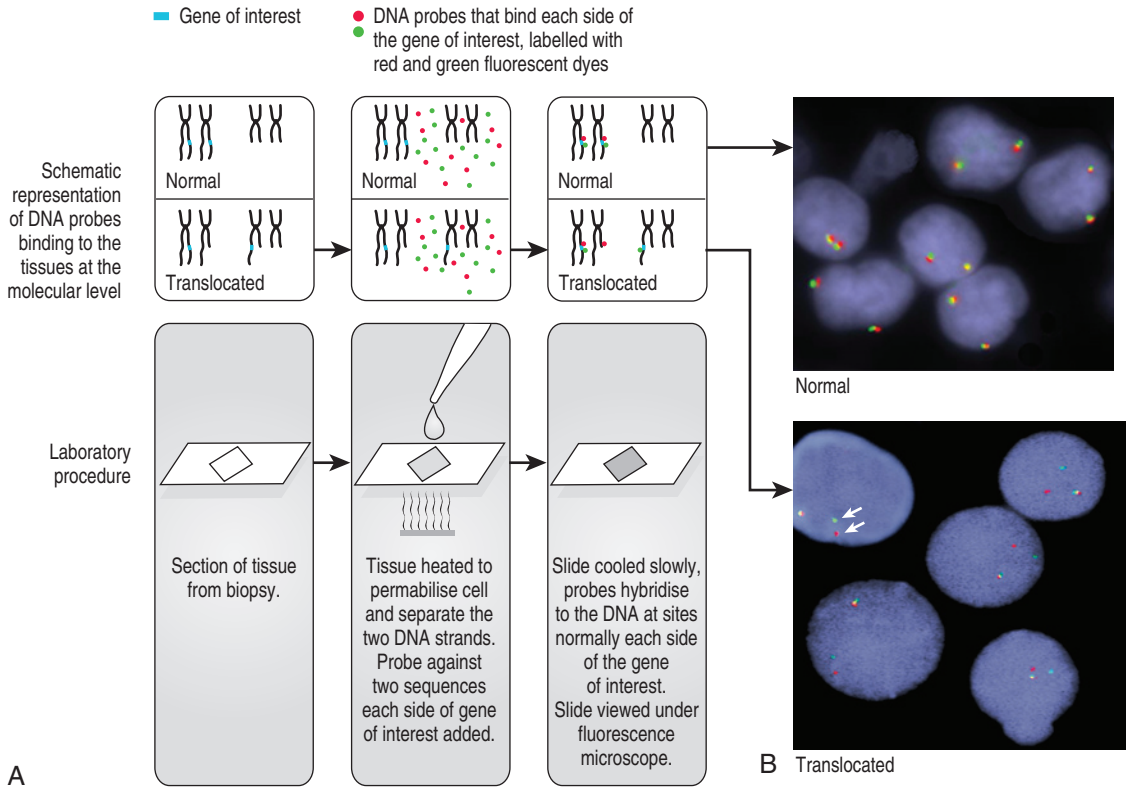


Fig. 1.11 (A) Method and application of in situ hybridisation to detect a chromosomal translocation using 'break apart' probes. (B) In this salivary carcinoma, the *myb* gene is translocated to another chromosome. In the normal cell the red and green probes are seen to bind to the DNA close together, each side of the *myb* gene. In the cell with the translocation, one copy of the gene is normal, but the other shows 'break apart' of the red and green probes, indicating a translocation involving a break point between the binding sites of the two probes within or close to the gene of interest. For the *myb* gene, this indicates that the carcinoma is an adenoid cystic carcinoma. When the red and green fluorescent spots are very close, the red and green colours merge to produce yellow. The background blue is a DNA-binding dye to show the nuclei.

Table 1.13 Types of blood test useful in oral diagnosis (see also Appendix 1.1)

Test	Main uses
'Full blood picture' usually includes erythrocyte number, size and haemoglobin indices and differential white cell count	Anaemia and the effects of sideropaenia and vitamin B_{12} deficiency associated with several common oral disorders. Leukaemias
Blood film	Leukaemias, infectious mononucleosis, anaemias
Erythrocyte sedimentation rate	Raised in systemic inflammatory and autoimmune disorders Particularly important in giant cell arteritis and Wegener's granulomatosis
Serum iron and total iron-binding capacity	Iron deficiency associated with several common oral disorders
Serum ferritin	A more sensitive indicator of body stores of iron than serum iron and total iron-binding capacity but not available in all laboratories
Red cell folate level	Folic acid deficiency is sometimes associated with recurrent aphthous ulceration and recurrent candidosis
Vitamin B_{12} level	Vitamin B_{12} deficiency is sometimes associated with recurrent aphthous ulceration and recurrent candidosis
Autoantibodies (e.g. rheumatoid factor, antinuclear factor, DNA-binding antibodies, SS-A, SS-B)	Raised in autoimmune diseases. Specific autoantibody levels suggest certain diseases
Viral antibody titres (e.g. Herpes simplex, Varicella zoster, mumps virus)	A rising titre of specific antibody indicates active infection by the virus
Paul–Bunnell or monospot test	Infectious mononucleosis
Syphilis serology	Syphilis
Complement component levels	Occasionally useful in diagnosis of systemic lupus erythematosus or familial angio-oedema
Serum angiotensin-converting enzyme	Sarcoidosis
Serum calcium, phosphate and parathormone levels	Paget's disease and hyperparathyroidism
Human immunodeficiency virus (HIV) test	HIV infection
Skeletal serum alkaline phosphatase	Raised in conditions with increased bone turnover, e.g. Paget's disease and hyperparathyroidism Lowered in hypophosphatasia

Table 1.14 Microbiological tests useful in oral diagnosis

Test	Main uses
Culture and antibiotic sensitivity	Detect unusual pathogens, e.g. actinomyces in soft tissue infection Antibiotic sensitivity for all infections, particularly osteomyelitis and acute facial soft tissue infection
Smear for candida	Candidosis
Viral culture or antigen screen	Viral culture identifies many viruses but requires considerable time Screening for viral antigen is faster but detects a more limited range of viruses

Box 1.15 Reminders for microbiological investigation

- Always take a sample of pus for culture and antibiotic sensitivity from bone and soft tissue infections *before* giving an antibiotic
- Always take the temperature of any patient with a swollen face, enlarged lymph nodes, malaise or other symptom or sign which might indicate infection
- Culture of *Candida* from the mouth does not necessarily indicate infection because this is a commensal organism. Demonstration of hyphae in a scraping of epithelial cells indicates active infection.

flora unless specialised anaerobic sampling and culture are performed. When antibiotic treatment fails, advice should be sought from a microbiologist as to whether this type of sampling may help.

Viral identification is rarely required for oral diseases because many oral viral infections are clinically typical and indicate the causative virus. A smear alone may show the nuclear changes of herpetic infection in epithelial cells from the margins of mucosal ulcers. A more sensitive and almost as rapid result may be obtained by sending a swab for virus detection using ELISA (enzyme-linked immunosorbent assay) or electron microscopy.

Key reminders for microbiological investigations are in Box 1.15.

Other clinical tests

Urine tests are valuable for the diagnosis of diabetes (suggested by repeated candidal or periodontal infection), kidney damage which can have resulted from autoimmune disorders such as Wegener's granulomatosis and for the detection of Bence-Jones protein in myeloma.

Taking the patient's temperature is an easily forgotten investigation. The temperature should be noted whenever bone or soft tissue infections are suspected. It helps distinguish facial inflammatory oedema from cellulitis and indicates systemic effects of infections and the need for more aggressive therapy.

Interpreting investigations and making a diagnosis and treatment plan

Check that the results of each investigation are compatible with the preliminary diagnosis. If a result appears at odds with other information, take into account the normal variation, perhaps with age or diurnal variation, and consider the possibility of false-positive and false-negative results. A common cause of unusual blood test results is a delay in transporting blood samples to the laboratory.

Further advice and specialised tests may be appropriate, but more extensive investigations, those carrying risks or radiation dose, are best organised through other medical specialties. In referrals, it is important to state whether the dentist is requesting the medical specialist to exclude a condition and refer the patient back, or to take over the investigation. If the latter, it is essential that dental causes have been completely eliminated as the cause of the problem.

Finally, ensure that the patient's notes include a complete record of the consultation and investigation results. This must be correctly dated, legible, limited to relevant facts and include a clear complaint history, list of clinical findings, test results and plan of treatment organised in a suitable form for quick reappraisal. It must be signed by the clinician and, in addition, the name should be printed below if the signature is anything less than perfectly legible. It should be possible for another person to continue to investigate or treat the patient without difficulty on the basis of the clinical record.

Photography or computerised video imaging is a very valuable adjunct to the clinical record. Pictures are especially useful in monitoring lesions that vary in the course of a long follow-up, for instance, white patches. It is useful to include teeth or a scale in the frame to allow accurate assessment of small changes in size. Photographs may also be helpful in explaining to patients about their condition and to show the effects of treatment, but consent for the intended uses of the photographs must be obtained first, and digital image files must be stored securely in the same way as other patient-identifiable digital files.

Appendix 1.1

Normal haematological values

Red cells		
Haemoglobin (adults)	Males 130–170 g/L	Females 115–165 g/L
Haematocrit (packed cell volume – PCV)	Males 0.40–0.54%	Females 0.36–0.47%
Mean cell volume (MCV)	80-100 fL	
Mean cell haemoglobin concentration (MCHC)	300–370 g/L	
Mean cell haemoglobin	27-32 pg	
Red cell count	Males 4.5–6.5 $\times 10^{12}$/L	Females 3.8–5.8 $\times 10^{12}$/L
Erythrocyte sedimentation rate (ESR)	Males 1-10 mm/h	Females 3-15 mm/h
White cells		
Total count	3.6–11 $\times 10^{9}$/L	
Neutrophils	1.8–7.5 $\times 10^{9}$/L	
Lymphocytes	1–4 $\times 10^{9}$/L	
Monocytes	0.2–0.8 $\times 10^{9}$/L	
Eosinophils	0.1–0.4 $\times 10^{9}$/L	
Platelets	140–400 $\times 10^{9}$/L	

Note. These reference ranges are for adults and are calculated assuming a normal distribution of results and excluding the upper and lower 2.5% of the range as abnormal. Therefore, approximately 5% of normal persons have values outside the figures quoted above. These are average values and may vary slightly between laboratories, and you should always check normal values with the testing laboratory.

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Disorders of tooth development 2

Development of an ideal dentition depends on many factors (Box 2.1).

Significant structural defects of teeth are much less common than irregularities of alignment of the teeth and abnormal relationship of the arches. The main groups of disorders affecting development of the dentition are summarised in Box 2.2 and Summary chart 2.1 and Summary chart 2.2.

ABNORMALITIES IN THE NUMBER OF TEETH

Anodontia

Total failure of development of a complete dentition (anodontia) is exceedingly rare. If the permanent dentition fails to form, the deciduous dentition is retained for many years. If the teeth survive caries, attrition will eventually destroy the crowns. Lack of alveolar bone growth may make implant placement difficult.

Isolated oligodontia

Oligodontia means few teeth. Failure of development of one or two teeth is relatively common and often hereditary. The teeth most frequently missing are third molars, second premolars or maxillary second incisors (Fig. 2.1), the last teeth in each series. Absence of third molars can be a disadvantage if first or second molars, or both, have been lost; otherwise, orthodontic problems of alignment and space loss are the only effects.

Absence of lateral incisors can sometimes be conspicuous because the large, pointed canines erupt in the front of the mouth beside the central incisors. It is often impossible to prevent loss of space, even if the patient is seen early. It is also difficult and time consuming to make space by orthodontic means to replace the laterals, so combined procedures with prosthodontic replacement are often used. Disguising the shape of the canines is destructive of the tooth, usually unconvincing cosmetically and produces a poor contact.

Genetic causes PMID: 25910507

General review PMCID: PMC3844689

Oligodontia or anodontia with systemic defects

Anhidrotic (hereditary) ectodermal dysplasia

The main features are summarised in Box 2.3. In severe cases, no teeth form. More often, most of the deciduous teeth form, but there are few or no permanent teeth. The teeth are usually peg-shaped or conical (Fig. 2.2).

When there is anodontia, the alveolar process, without teeth to support, fails to develop and has too little bone to support standard implants without surgical bone augmentation. The profile then resembles that of an elderly person because of the gross loss of vertical dimension. The hair is fine and sparse (Fig. 2.3), particularly in the tonsural region. The skin is smooth, shiny and dry due to absence of sweat glands. Heat is therefore poorly tolerated. The finger nails are usually also defective. As a temporary measure, dentures or overdentures are usually well tolerated by children.

Box 2.1 Requirements for development of an ideal dentition

- Formation of a full complement of teeth
- Normal structural development of the dental tissues
- Eruption of each group of teeth at the appropriate time into an adequate space
- Normal development of jaw size and relationship
- Eruption of teeth into correct relationship to occlude with their opposite numbers
- Maintenance of tooth position by normal soft tissue size and pressure

Box 2.2 Disorders of development of teeth

- Abnormalities in number
 - Anodontia or oligodontia (hypodontia)
 - Additional teeth (hyperdontia)
- Disorders of eruption
- Defects of structure
 - Enamel defects
 - Dentine defects
 - Cementum defects
- Developmental anomalies of several dental tissues
- Developmental anomalies of dental tissues and adjacent bone
- Intrinsic pigmentation
- Odontomes



Fig. 2.1 Congenital absence of lateral incisors with spacing of the anterior teeth.

Box 2.3 Anhidrotic ectodermal dysplasia: major features

- Usually a sex-linked recessive trait
- Hypodontia
- Hypotrichosis (scanty hair)
- Anhidrosis (inability to sweat)



Fig. 2.2 Anhidrotic ectodermal dysplasia showing conical teeth.

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Please refer to the printed publication.

Fig. 2.3 Another case showing typical fine and scanty hair and loss of support for the facial soft tissues.

Implants cannot be placed in the maxilla during growth, but it may be possible to use mini implants or implants in the anterior mandible from a young age because, without teeth to erupt, alveolar growth is complete. Ultimately, a tooth-supported fixed partial denture or implant-supported overdenture is often a good solution.



Fig. 2.4 A paramolar, a buccally placed supernumerary molar tooth.

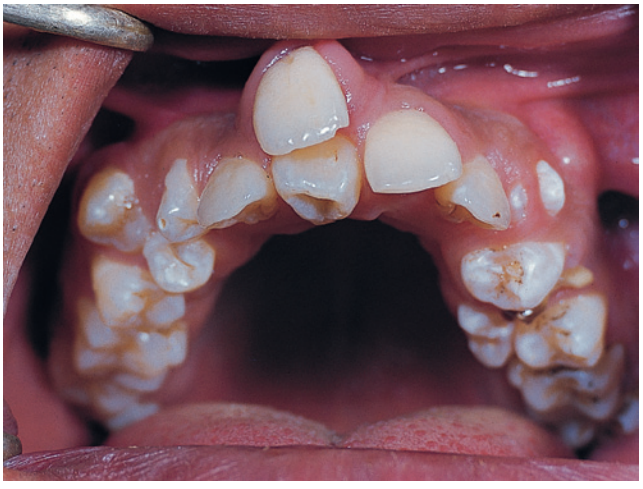


Fig. 2.5 Maleruption of a midline tuberculate supernumerary and two supplemental premolars.

Web URL 2.1 Ectodermal dysplasia URL: http://rarediseases.org/rare-diseases/hypohidrotic-ectodermal-dysplasia/

Other conditions associated with oligodontia

There are many rare syndromes in which oligodontia is a feature, but the only common one is Down's syndrome (Ch. 39). One or more third molars are absent in more than 90% of these patients, and absence of individual teeth is also common. Anodontia is rare.

Additional teeth: hyperdontia

Additional teeth are relatively common. They are usually of simple conical shape but less frequently resemble teeth of the normal series. These are the results of organised development and maturation under genetic control, not simple excessive growth of the dental lamina.

Supernumerary teeth This term is used for any additional tooth (Fig. 2.4). Conical or more seriously malformed additional teeth most frequently form in the incisor or molar region and, very occasionally, in the midline (mesiodens, Fig. 2.5).

Supplemental teeth These are supernumerary teeth with a normal morphology, and they are usually an extra tooth at the end of the incisor, premolar or molar series (also seen in Fig. 2.5).

Effects and treatment

Additional teeth usually erupt in abnormal positions, labial or buccal to the arch, creating stagnation areas and greater susceptibility to caries, gingivitis and periodontitis. Alternatively, a supernumerary tooth may prevent a normal tooth from erupting or cause crowding and malalignment. These additional teeth are usually best extracted.

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Syndromes associated with hyperdontia

These syndromes are all rare, but probably the best known is cleidocranial dysplasia (Ch. 13), in which many additional teeth develop but fail to erupt.

DEFECTIVE ENAMEL FORMATION

Structural defects of the teeth, such as pitting, discoloration or more serious defects can only arise during development and are, therefore, markers of past disease. Hypoplasia of the teeth is not an important contributory cause of dental caries. Only normally formed enamel can become carious, and hypoplasia due to fluorosis is associated with enhanced resistance.

Defects of deciduous teeth

Calcification of deciduous teeth begins at approximately the fourth month of intrauterine life. Disturbances of metabolism or infections that affect the fetus at this early stage without causing abortion are rare. Defective structure of the deciduous teeth is therefore uncommon but, in a few places, such as parts of India, where the fluoride content of the water is excessively high, the deciduous teeth may be mottled.

The deciduous teeth may be discoloured by abnormal pigments circulating in the blood. Severe neonatal jaundice may cause the teeth to become yellow, or there may be bands of greenish discoloration. In congenital porphyria, a rare disorder of haemoglobin metabolism, the teeth are red or purple. Tetracycline given during dental development, contrary to guidelines, is now a rare cause of permanent discoloration.

Defects of permanent teeth

Single permanent teeth may be malformed as a result of local causes such as periapical infection of a predecessor (Turner teeth – Fig. 2.6), or trauma from intubation while a preterm neonate (Fig. 2.7). Multiple affected teeth usually indicate previous systemic disease as summarised in Box 2.4.

Amelogenesis imperfecta

→ Summary chart 2.1 p. 26

Amelogenesis imperfecta is a group of conditions caused by defects in the genes that encode enamel matrix proteins or other proteins or enzymes required to process or mineralise the matrix. Classification is complex and based on

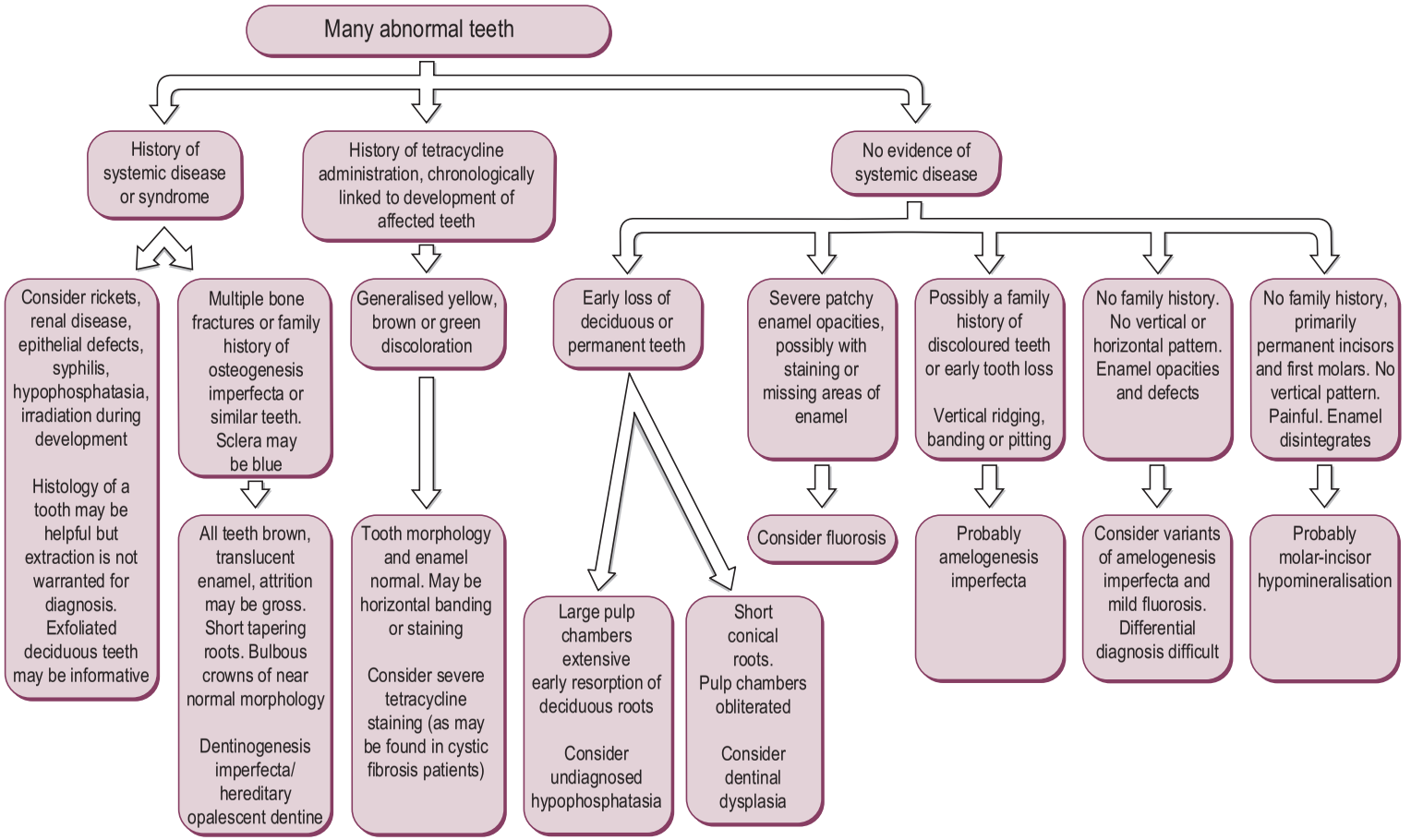


Fig. 2.6 Turner tooth, a hypoplastic tooth resulting from periapical infection, usually of a deciduous predecessor.

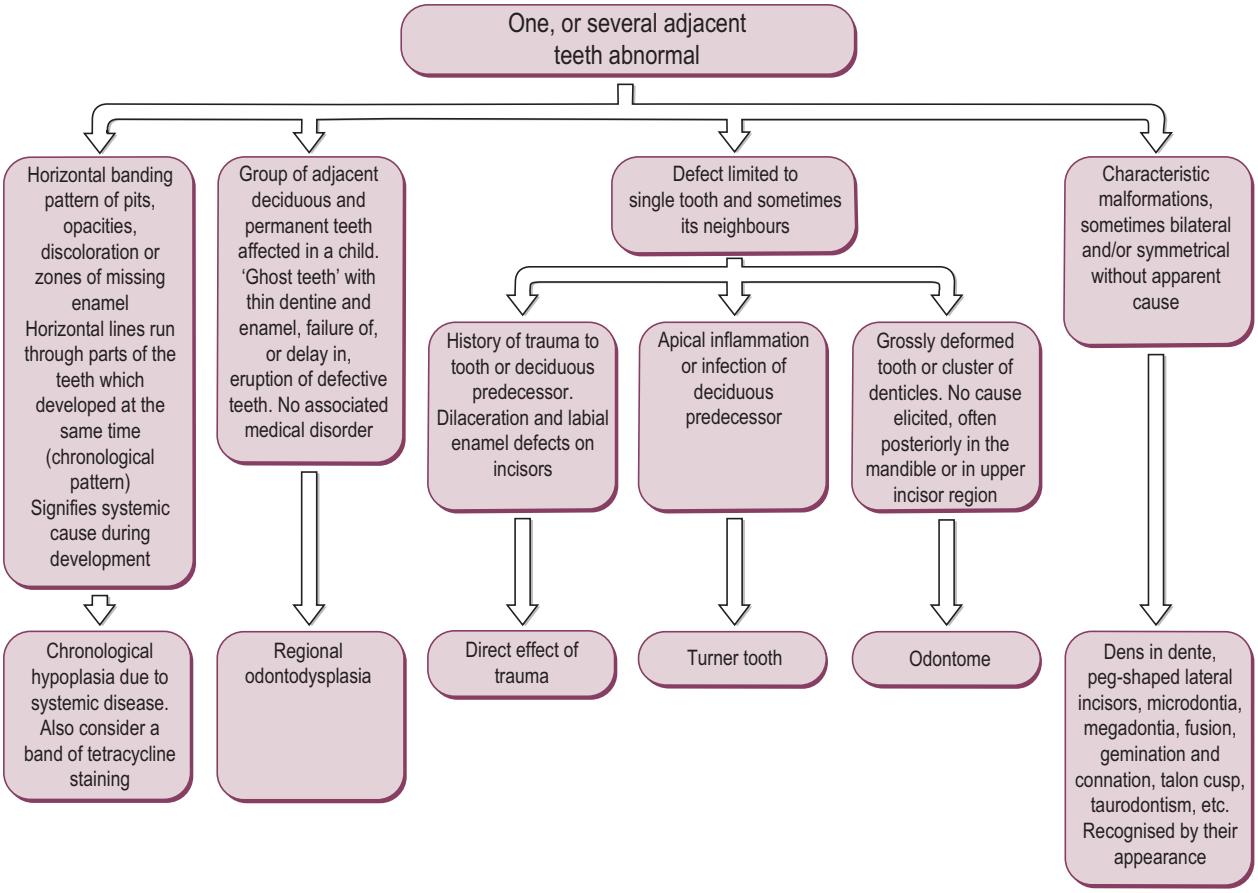


Fig. 2.7 Localised dental disturbance caused by prolonged intubation during tooth development. The upper left central incisor shows enamel pitting incisally, and the upper right central incisor is deformed and has failed to erupt.

Summary chart 2.1 Differential diagnosis of developmental defects of the teeth.



Summary chart 2.2 Differential diagnosis of developmental and acquired abnormalities of one or a group of teeth.



pattern of inheritance, type of defect (enamel hypoplasia, hypomineralisation or hypomaturation) and appearance (smooth, rough or pitted). At least 16 forms have been recognised on clinical grounds, but some are the same genetic condition with differing severity, and the classification is contentious.

Inheritance can be autosomal dominant, recessive or X-linked. However, the most common types have an autosomal inheritance and are thought to be caused by mutations in the genes for ameloblastin (C4), or genes for enamelin (C4) or tuftelin (C1). In the case of the autosomal dominant type of amelogenesis imperfecta, the defective gene is enamelin (C4).

The less common X-linked types are caused by a variety of defects in the AMELX genes encoding amelogenin, located on the X and Y chromosomes (the copy on the Y gene being inactive) and, confusingly, it seems the same mutation can sometimes cause hypoplasia, hypomineralisation or hypomaturation in different patients.

Genetic factors act throughout the whole duration of amelogenesis. Characteristically, therefore, all teeth are affected, and defects involve the whole enamel or randomly distributed patches of it. By contrast, exogenous factors affecting enamel formation (with the important exception of fluorosis) tend to act for a relatively brief period and produce defects related to that period of enamel formation (a chronological pattern).

Until there is a better understanding, dentists should at least be able to identify the three clinical types of hypoplasia, hypocalcification and hypomaturation and take a family history, which may reveal an inheritance pattern.

Review types causes PMCID: PMC1847600

Hypoplastic amelogenesis imperfecta

The main defect in this type is deficient formation of matrix, so that the amount of enamel is reduced but normally mineralised. The enamel is randomly pitted, grooved or uniformly very thin, but hard and translucent (Fig. 2.8). The defects tend to become stained, but the teeth are not especially susceptible to caries unless the enamel is scanty and fractures to expose dentine.

The main patterns of inheritance are autosomal dominant and recessive, X-linked and (a genetic rarity) an X-linked dominant type. In the last type, there is almost complete failure of enamel formation in affected males, whereas in females the enamel is vertically ridged (Figs 2.9–2.12). Occasionally, cases are difficult to classify (Fig. 2.13).

Hypomaturation amelogenesis imperfecta

The enamel is normal in thickness on eruption but with opaque, white to brownish-yellow patches caused by failure of maturation, a process of matrix removal and increasing mineralisation that is partly developmental and partly post-eruptive. The appearance can mimic fluorotic mottling if the spots are small (Figs 2.14 and 2.15). However, affected enamel is soft and vulnerable to attrition, though not as severely as the hypocalcified type.



Fig. 2.8 Amelogenesis imperfecta, hypoplastic pitted type. Enamel between pits appears normal.

Box 2.4 Multiple malformed permanent teeth: important causes

Genetic

- Amelogenesis imperfecta
 - Hypoplastic
 - Hypomaturation
 - Hypocalcified
- Chronological hypoplasia
- Molar-incisor hypomineralisation
- Dentinogenesis imperfecta
 - Shell teeth
- Dentinal dysplasia
- Regional odontodysplasia
- Multisystem disorders with associated dental defects
- Hypophosphatasia

Infective

- Congenital syphilis

Metabolic

- Rickets
- Hypoparathyroidism

Drugs

- Tetracycline pigmentation
- Cytotoxic chemotherapy

Fluorosis

Other acquired developmental anomalies

- Fetal alcohol syndrome



Fig. 2.9 Close-up of X-linked dominant hypoplastic type amelogenesis imperfecta. These teeth, from an affected female, show the typical vertical ridged pattern of normal and abnormal enamel as a result of Lyonisation.



Fig. 2.10 Amelogenesis imperfecta X-linked dominant hypoplastic form in a male. This premolar has a cap of enamel so thin that the shape of the crown is virtually that of the dentine core.

There are several variants of hypomaturation defects such as a more severe, autosomal dominant type combined with hypoplasia and milder forms limited to only some tooth surfaces.

Hypocalcified amelogenesis imperfecta

Enamel matrix is formed in normal quantity but is poorly calcified. When newly erupted, the enamel is normal in thickness and form, but weak or chalky and opaque in appearance.

The teeth tend to become stained, and enamel is relatively rapidly worn away. The upper incisors may acquire a shoulder due to the chipping away of the thin, soft enamel of the incisal edge (Fig. 2.16). There are dominant and recessive patterns of inheritance.



Fig. 2.11 Amelogenesis imperfecta X-linked dominant hypoplastic type in a male showing a thin translucent layer of defective enamel on the dentine surface.



Fig. 2.12 Amelogenesis imperfecta, hypoplastic type. In this pitted hypoplastic type, the pits are seen to be focal areas of reduced enamel formation with incremental lines diverted around them. No enamel has been lost from the pit.

Chronological hypoplasia

➔ Summary chart 2.1 p. 26

Any severe disturbance of metabolism can halt enamel formation. Dentine formation is less sensitive to insult, so tooth formation will usually continue to produce a normally shaped tooth with only a band of enamel missing. The usual causes are the childhood fevers or severe infantile gastroenteritis. Measles with severe secondary bacterial infection used to be the most common cause of this limited type of dental defect, but such defects have become uncommon since measles vaccination.

Unlike inherited forms of hypoplasia, only a restricted area of enamel is missing, corresponding to the sites of development at the time of the illness.



Fig. 2.13 Amelogenesis imperfecta, indeterminate type. Some cases, such as this, are difficult to classify but are clearly inherited, as shown by their long family history.



Fig. 2.14 Amelogenesis imperfecta, hypomaturation type. Tooth morphology is normal, but there are opaque white and discoloured patches.



Fig. 2.15 Amelogenesis imperfecta, one of the several hypomaturation types. In this form there are opaque white flecks and patches affecting the occlusal half of the tooth surface.



Fig. 2.16 Amelogenesis imperfecta, hypocalcified type. The soft chalky enamel was virtually of normal thickness and form but has chipped away during mastication leaving a characteristic shoulder, seen best on the upper left central incisor.



Fig. 2.17 Chronological hypoplasia due to metabolic upset. Unlike the hereditary types of amelogenesis imperfecta, defects are linear and thought to correspond to a short period of amelogenesis disturbed by a concurrent severe illness.

Clinically, the typical effect is one or more rows of horizontally disposed pits, grooves or a completely missing band of enamel horizontally across the crowns of the teeth. Defects are usually in the incisal third of incisors, suggesting that the disorder had its effect during the first year or two of life, when such infections cause the most severe systemic upset (Fig. 2.17). Metabolic disturbance *in utero* or around birth affects the primary teeth in addition (Fig. 2.18). The horizontal pattern is important in distinguishing chronological hypoplasia from genetic causes of hypoplasia and determining the timing of the systemic disease (Fig. 2.19).

Molar-incisor hypomineralisation

➔ Summary chart 2.1 p. 26

Molar incisor hypomineralisation is an unexplained, apparently recently recognised and increasingly frequent condition defined by hypomineralisation of all first permanent molars and incisors (Fig. 2.20). The teeth erupt normally and have patchy opaque and yellow brown patches on the enamel of the occlusal third of the crowns.

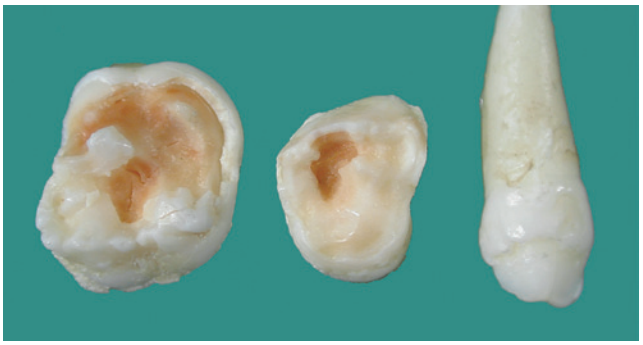


Fig. 2.18 Chronological hypoplasia with loss of primary molar occlusal enamel and a horizontal ridge on the upper canine.

The enamel surface is hard, but the underlying enamel is soft and breaks down, leaving a stained rough and soft surface that is prone to caries. The defects are sharply demarcated.

The cause is probably failure of enamel maturation, but the presentation and family history are distinct from amelogenesis imperfecta and chronological hypoplasia. It appears that many cases are similar to chronological hypoplasia in aetiology, but the systemic upset is milder and insufficient to cause the more severe defect of hypoplasia. A very wide range of types of illness appear to be able to cause hypomineralisation.

Molars are usually worse affected than incisors. The affected teeth are hypersensitive and difficult to anaesthetise. Restorations often fail, partly due to the adverse crown shape and partly because the enamel is not amenable to use of adhesive materials, even away from the clinically detectable defects. This makes treatment difficult, and after a period of preventive care to remineralise the molars and preserve them as space maintainers, extraction is often the best course of action. Otherwise full coverage restorations are required. Microabrasion is not sufficient to restore most affected incisors because the soft enamel extends deeply, and restorations or veneers are usually required.

Web URL 2.2 Review and treatment: http://www.aapd.org/assets/1/25/william2-28-3.pdf

Treatment PMID: 16805354, 26856002 and 23410530

Nature of enamel defect PMID: 23685033

DEFECTIVE DENTINE FORMATION

➔ Summary chart 2.1 p. 26

The classification of hereditary dentine defects is unsatisfactory. As in amelogenesis imperfecta, the genetic findings do not correlate well with clinical presentation, and terminology is used inconsistently. The previous widely used classifications (of Witkop and of Shields) are now considered redundant, but no replacement is yet established.

The term *dentinogenesis imperfecta* (type I) was used when abnormal teeth were associated with bone defects, but this combination is now classified as *osteogenesis imperfecta*. The term dentinogenesis imperfecta is used when only the teeth are involved, replacing the term *hereditary opalescent dentine*.

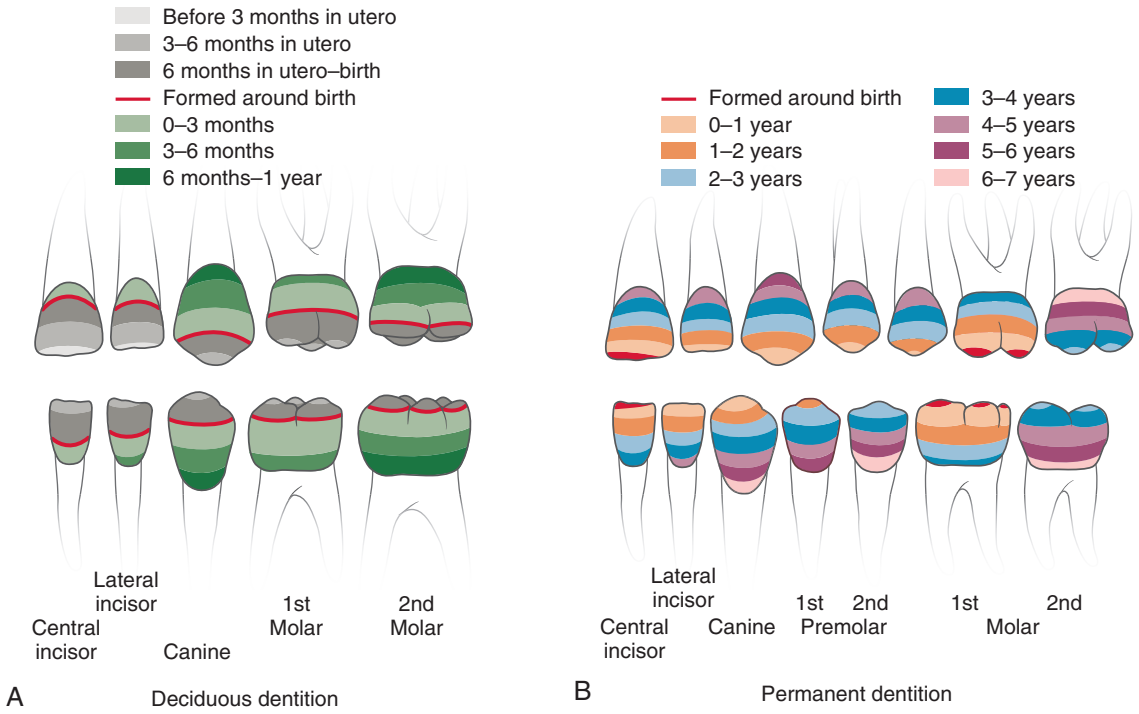


Fig. 2.19 Charts to determine the chronology of enamel hypoplasia. Chronological hypoplasia should affect many teeth symmetrically consistent with the time of illness.



Fig. 2.20 **Molar-incisor hypomineralisation.** Typical appearance with discolouration and breakdown of enamel almost exclusively on permanent incisors and first molars.

Osteogenesis imperfecta with opalescent teeth → Summary chart 2.1 p. 26

This uncommon defect of collagen formation disturbs formation of both bone and dentine. Many forms are known, and the condition is described in Chapter 13. Types III and IV are those most frequently associated with dentine defects. Both are autosomal dominant traits with mutation in the genes COL1A1 and COL1A2 that prevent the procollagen alpha helix polymerising into normal type 1 collagen. The dentine is soft and has abnormally high water content.

In both these types, opalescent teeth are present in over 80% of patients in the primary dentition. Tooth discoloration and attrition is often most striking in the deciduous dentition. Class III malocclusion is associated in over 70% of patients. In type III disease, dental development is delayed in 20% but, in type IV disease, it is accelerated in over 20% of patients.

Dentinogenesis imperfecta

→ Summary chart 2.1 p. 26

This condition produces identical changes in appearance and structure of the teeth to those in osteogenesis imperfecta but is caused by mutations in dentine sialoprotein, a dentine matrix protein, rather than collagen genes. Previously there were thought to be two types (types II and III), but the condition of shell teeth is now thought to be just a more severe presentation of type II caused by defects in the same gene. Dentinogenesis imperfecta can be associated with developmental hearing loss.

Clinical features

The enamel appears normal but uniformly brownish or purplish and abnormally translucent (Fig. 2.21), giving an opal-like appearance that leads to the clinical description of 'hereditary opalescent dentine'. The appearance is caused by the dark dentine being visible through the enamel, which is usually normal but may have hypoplastic defects in a minority of patients. The shape and size of the crowns is essentially normal, but the roots are slender and stunted, giving the tooth a cervical constriction and bulbous outline radiographically (Fig. 2.22). Dentine formation progresses to obliterate the pulp chamber at an early age. There is a



Fig. 2.21 Dentinogenesis imperfecta. Showing the grey-brown translucent appearance of the teeth which are of normal morphology.



Fig. 2.23 Dentinogenesis imperfecta. In this 14-year-old, the teeth have worn down to gingival level, but the pulp chambers have become obliterated as part of the disease process. A rim of enamel remains around the necks of the posterior teeth.

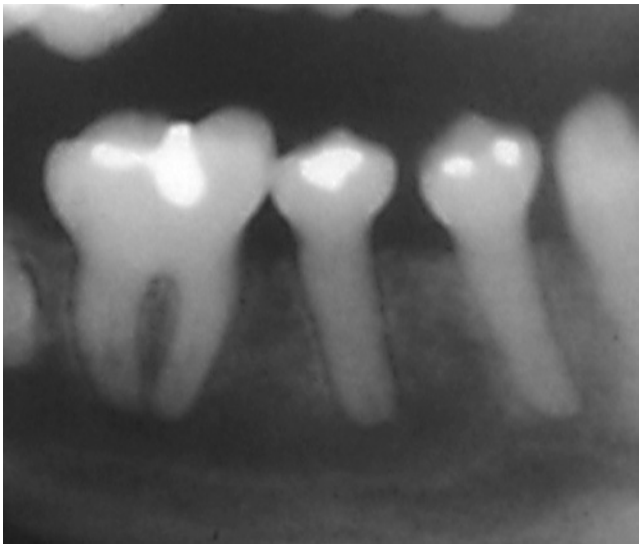


Fig. 2.22 Dentinogenesis imperfecta. Showing the slender roots and bulbous crowns of the 'tulip-shaped' teeth.

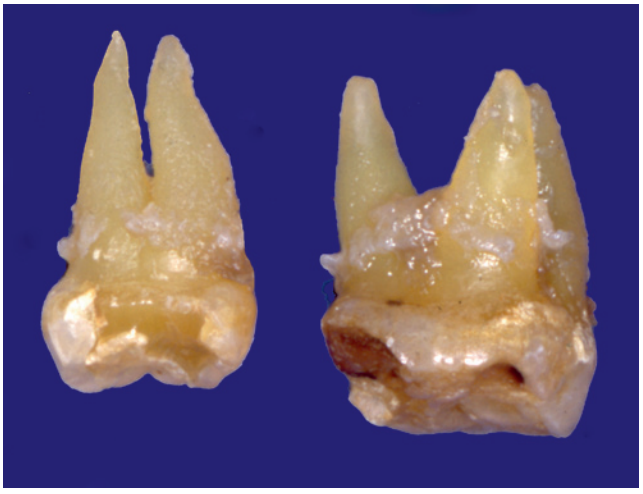


Fig. 2.24 Dentinogenesis imperfecta. Slender tapering roots and loss of enamel through fracturing.

weak zone in the dentine just below the amelodentinal junction, and the lack of resilient dentine to support the enamel allows enamel to chip away, exposing the dentine, which is soft and rapidly wears away, eventually to the gingivae (Figs 2.23 and 2.24). In some patients, only a few teeth are severely affected, whereas the remainder appear normal.

Treatment aims to preserve vertical dimension, avoid extractions to prevent space loss and allow normal alveolar bone growth for implants later. Early application of occlusal composite onlays and preformed metal crowns on molars reduce wear. Worn roots may be used as temporary overdenture abutments but are too soft to survive long.

Severely affected patients may have shell teeth, with only a thin outer mantle layer of dentine tissue surrounding overlarge pulp chambers. Shell teeth are very difficult to manage conservatively.

Tooth structure

The earliest-formed dentine under the amelodentinal junction usually appears normal. There is a sharp junction with the deeper defective dentine. This has few tubules, and they run in disorganised patterns. The uniform structure of dentine is absent; extensions of the pulp penetrate the dentine almost to the enamel (Fig. 2.25) and can be exposed by attrition to devitalise the teeth. Calcification is incomplete and the dentine soft.

The pulp chamber becomes obliterated early, and odontoblasts degenerate. Cellular inclusions in the dentine are common. In shell teeth, the dentine layer is very thin (Fig. 2.26).

Review PMCID: PMC2600777

Dentinal dysplasia ('rootless' teeth)

➔ Summary chart 2.1 p. 26

Dentinal dysplasia (previously type 1 but now the only type)

In this rare disorder, the crowns are of normal shape and size, but the roots are either absent or very short and conical. The pulp chambers are obliterated by multiple nodules of poorly organised dentine containing tubules running in sheaves. A range of pulp shapes can result from differing severity, with almost complete obliteration producing crescent-shaped pulp at the level of the floor of the normal chamber. In the worst affected teeth, roots are absent. Teeth tend to be lost early in life (Fig. 2.27). There are pulpal extensions through dentine to the enamel, and vitality is

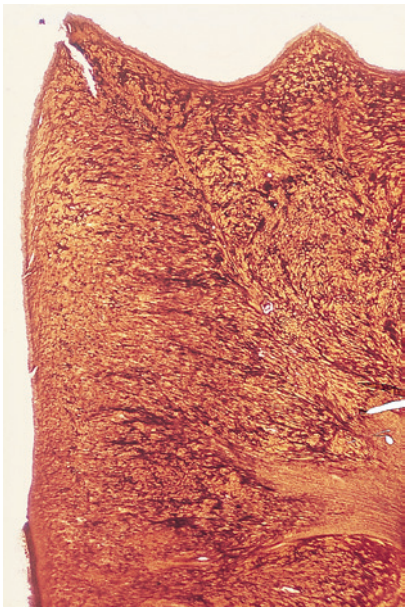


Fig. 2.25 Microscopic appearance of dentinogenesis imperfecta showing the grossly disorganised tubular structure with inclusions of pulp in the dentine and obliteration of the pulp cavity.



Fig. 2.28 **Dentinal dysplasia.** The pulp chamber in the short, broad root is obliterated by nodules of dentine with swirling patterns of tubules.

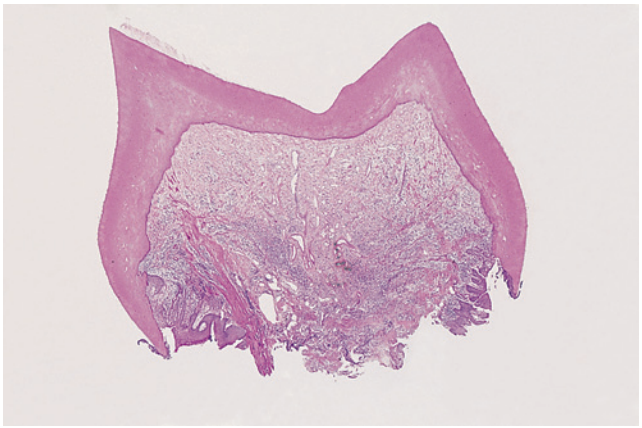


Fig. 2.26 **Shell tooth.** In this severe form of dentinogenesis imperfecta, only a thin mantle of dentine is formed, and no root develops.



Fig. 2.27 **Dentinal dysplasia type 1.** Radiograph showing short roots, spontaneous pulp necrosis with apical areas, and obliterated crescent-shaped pulps.

lost quickly; otherwise the lack of roots predisposes to periodontitis.

The coronal dentine and enamel are normal or almost so, but dentinal tubule patterns in the root are abnormal (Fig. 2.28). Both dentitions are affected, the deciduous more severely.

Dentinal dysplasia 'type 2'

The defect in this rare disorder is in the dentine sialoprotein gene, so this disorder is better classified as a severely affected form of dentinogenesis imperfecta. The tooth crowns have the same opalescent appearance as dentinogenesis imperfecta in the deciduous dentition. The permanent dentition appears normal or nearly normal in colour, but the pulps are larger than normal. A tall, wide coronal pulp extends high into the crown (thistle pulp), sometimes with pulp stones, and more marked in the permanent dentition (Fig. 2.29).

Review PMCID: PMC2600777

DEFECTS OF ENAMEL AND DENTINE

→ Summary chart 2.1 p. 26

Regional odontodysplasia (ghost teeth)

→ Summary chart 2.2 p. 27

This localised disorder of development affects a group of teeth in which there are severe abnormalities of enamel, dentine and pulp. The disorder is not hereditary, and the aetiology is unknown. A few cases have been associated with facial vascular naevi or abnormalities such as hydrocephalus. There is no sex or racial predilection.

Clinically, regional odontodysplasia may be recognisable at the time of eruption of the deciduous teeth (2–4 years) or of the permanent teeth (7–11 years). The maxillary teeth are most frequently affected. Either or both dentitions, and one or, at most, two quadrants may be affected. The abnormal teeth frequently fail to erupt but, if they do, show yellowish deformed crowns with a rough surface.



Fig. 2.29 Dentinogenesis imperfecta of dentinal dysplasia type 2 presentation. The pulp chambers are rounded, tall and wide in the developing dentition. The classical 'thistle-shaped' pulp appearance is seen in the lower canine and premolars.



Fig. 2.30 Radiographic appearance of regional odontodysplasia. In the anterior regions the condition usually stops at the midline.

Affected teeth have very thin enamel and dentine surrounding a greatly enlarged pulp chamber. In radiographs, the teeth appear crumpled and abnormally radiolucent or hazy, due to the paucity of dental hard tissues, explaining the term 'ghost teeth' (Figs 2.30 and 2.31).

Histologically, the enamel thickness is highly irregular and lacks a well-defined prismatic structure. The dentine, which has a disorganised tubular structure, contains clefts and interglobular dentine mixed with amorphous mineralised tissue. The surrounding follicle soft tissue may contain small calcifications (Figs 2.33–2.34).

If they erupt, the teeth are susceptible to caries and fracture. If they can be preserved and restored, crown and root dentine continue to form, and the teeth may survive long enough to allow normal development of the alveolar ridge and occlusion. However, extractions are often required eventually. This should not be done until it is certain that eruption has completely failed or the defects are too severe to be treatable.

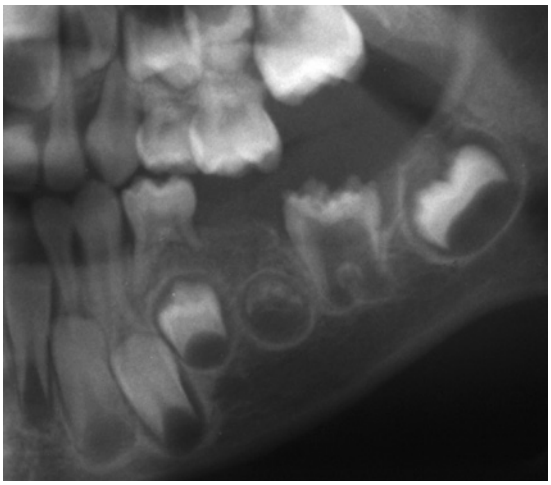


Fig. 2.31 Radiographic appearance of regional odontodysplasia. The lower left 5 and 6 are affected. Note their abnormal outline and radiodensity by comparison with the 4 and 7.

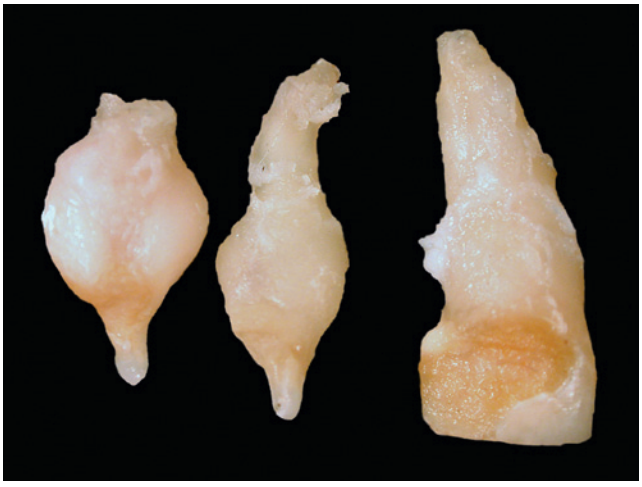


Fig. 2.32 Regional odontodysplasia. Distorted and hypoplastic teeth from the case shown in Fig. 2.30.

Review and cases PMID: 2549236

Cases PMID: 9524463

Natural history and treatment PMID: 17613259

Segmental odontomaxillary dysplasia

This rare disorder may be a mild form of the genetic condition hemimaxillofacial dysplasia; it can be mistaken for fibrous dysplasia or regional odontodysplasia.

Segmental odontomaxillary dysplasia causes unilateral expansion of the alveolar process of the maxilla in a child in the primary or mixed dentition. The premolar and molar regions are most frequently affected. Enlargement is due to both fibrous enlargement of the gingiva and swelling of the alveolar bone. The antrum is small, and the maxilla is distorted, although only rarely to the extent of causing facial asymmetry. Eruption of teeth in the affected area is delayed, and they are hypoplastic to varying degrees, with enlargement of the pulps, thin pitted enamel, an irregular pulp/dentine interface and many pseudoinclusions in poorly organised dentine, and pulp stones. Permanent successors, particularly the premolars, may be absent.

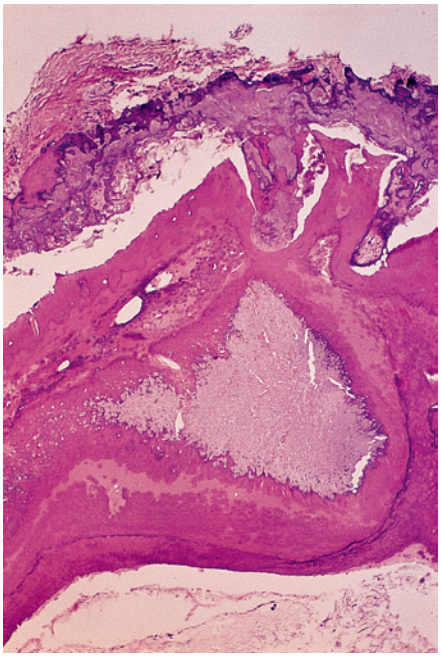


Fig. 2.33 Regional odontodysplasia. Both enamel and dentine are deformed, and there is calcification of the reduced enamel epithelium seen as a dark blue line at the top of the image.



Fig. 2.34 Regional odontodysplasia. Showing dysplastic dentine with a disorganised tubule structure, an irregular enamel space and mineralised enamel epithelium.

Radiographically, there is a zone of bone sclerosis with a coarse trabecular pattern and loss of the cortex and missing and distorted teeth (Fig. 2.35). Histologically, the sclerotic zone consists of woven bone trabeculae in bland fibrous tissue and appears superficially similar to the regressing stage of fibrous dysplasia. Both radiographs and histology are therefore necessary for diagnosis.

Case series PMID: 21684782



Fig. 2.35 Segmental odontomaxillary dysplasia. Showing abnormal upper primary molars that are indistinct against a background of even, coarsely trabecular bone. Permanent successors are absent.

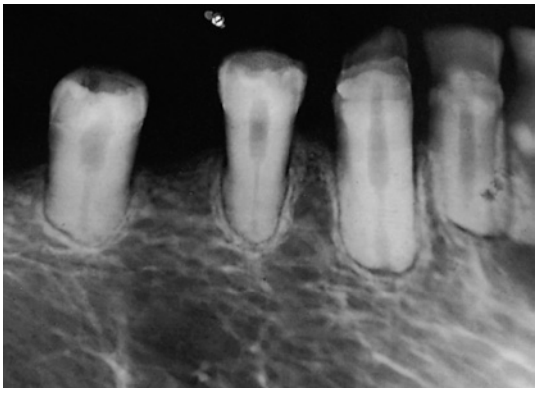


Fig. 2.36 Teeth in childhood hypoparathyroidism with short blunt roots, open apices and large pulp chambers.

OTHER SYSTEMIC DISEASES AFFECTING TEETH

Other metabolic disturbances

Rickets can cause hypocalcification of the teeth, but only if unusually severe (see Ch. 13).

Early-onset idiopathic hypoparathyroidism is rare. Ectodermal effects are associated. The teeth may therefore be hypoplastic with ridged enamel, short blunt roots and persistently open apices (Fig. 2.36). The nails may be defective, and there may be complete absence of hair. Patients with early-onset idiopathic hypoparathyroidism may later develop other endocrine deficiencies (polyendocrinopathy syndrome), and chronic oral candidosis may be the first sign (Ch. 15).

Hypophosphatasia. This rare genetic disorder can have severe skeletal effects as a result of failure of development of mature bone. There may also be failure of cementum formation causing early loss of teeth (Fig. 2.37). In milder forms, premature loss of the deciduous incisors is characteristic and occasionally the only overt manifestation of the disease.

Hypophosphatasia dental effects PMID: 19232125



Fig. 2.37 Tooth in hypophosphatasia showing the enlarged pulp chamber and absence of cementum.

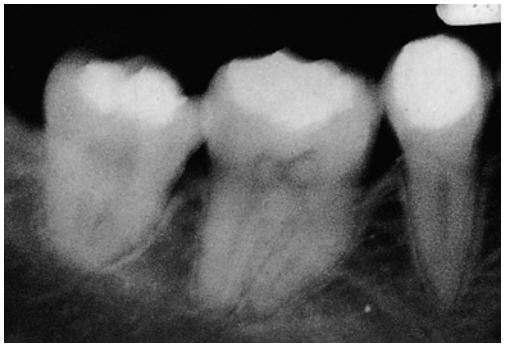


Fig. 2.38 Multiple pulp stones in a case of Ehlers–Danlos syndrome.

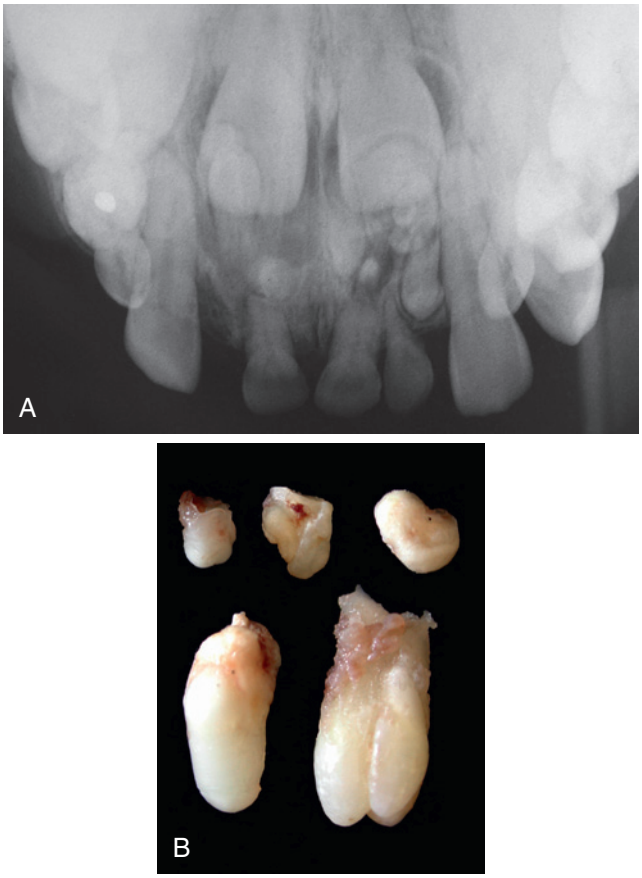


Fig. 2.39 **Gardner's syndrome.** Multiple unerupted abnormally formed supernumerary teeth. See also Fig. 12.16.

Ehlers–Danlos syndromes

This group of collagen disorders is characterised (to varying degrees) by hypermobile joints, loose hyperextensible skin, fragile oral mucosa and, in type VIII, early-onset periodontitis. There may also be temporomandibular joint symptoms such as recurrent dislocation (see main section in Ch.14).

The main dental abnormalities are small teeth with short roots and multiple pulp stones (Fig. 2.38).

Gardner's syndrome (familial adenomatous polyposis)

The Gardner variant of familial adenomatous polyposis (often referred to as Gardner's syndrome) is characterised by multiple osteomas, especially of the jaws, colonic polyps and skin tumours. The majority of patients have dental abnormalities. These include impacted teeth other than third molars, supernumerary or missing teeth and abnormal root formation (Fig. 2.39). This syndrome is discussed and illustrated further in Chapter 12.

Colon carcinoma develops in almost all patients by middle age, and the mortality is high. The dental abnormalities can be detected in childhood or adolescence, and recognition of this syndrome may be life saving.

Epidermolysis bullosa

Epidermolysis bullosa is a genetic blistering disease of skin and mucosae (Ch. 16). Dental abnormalities include fine or coarse pitting defects, or thin and uneven enamel, which may also lack prismatic structure. The amelodentinal junction may be smooth. Dental defects vary in the different subtypes of the disease but are most frequent in the autosomal recessive, scarring type of epidermolysis bullosa in which there may be delayed, or failure of, eruption. The defects result from poor adhesion between ameloblasts during development.

Congenital syphilis ➔ Summary chart 2.1 p. 26

Prenatal syphilis, the result of maternal infection, can cause a characteristic dental deformity, described by Hutchinson in 1858.

If the fetus becomes infected at a very early stage, abortion follows. Infants born with stigmata of congenital syphilis result from later fetal infection, and only the permanent teeth are affected. The characteristic defects are usually seen in the upper central incisors.

The incisors (Hutchinson's incisors) are small, barrel-shaped and taper toward the tip (Fig. 2.40). The incisal edge sometimes shows a crescentic notch or deep fissure which forms before eruption and can be seen radiographically. An anterior open bite is also characteristic. The first molars may be dome shaped (Moon's molars) or may have a rough pitted occlusal surface with compressed nodules instead of cusps (mulberry molars) (Fig. 2.41). These defects are often thought largely of historical interest, but congenital syphilis has reappeared in developed countries including the UK. Several hundred cases of congenital syphilis occur every year in the United States, and worldwide half a million infants die from it every year.



Fig. 2.40 Congenital syphilis: Hutchinson's teeth. The characteristics are the notched incisal edge and the peg shape tapering from neck to tip. *(From Cawson RA et al, 2001.* Oral disease. *3rd ed. St Louis: Mosby.)*



Fig. 2.41 Congenital syphilis: Molars. The molar on the left is a mulberry or Fournier molar with cusps surrounded by a hypoplastic groove producing a knobbly surface. That on the right is a Moon's molar, with a smooth rounded crown that tapers toward the occlusal surface. *(Copyright Museums at the Royal College of Surgeons.)*

The effects are due to infection of the dental follicle by *Treponema pallidum*. The postulated consequences are chronic inflammation, fibrosis of the tooth sac, compression of the developing tooth and distortion of the ameloblast layer. *T. pallidum* and inflammation are thought to cause proliferation of the odontogenic epithelium, which bulges and kinks into the dentine papilla, causing the characteristic central notch.

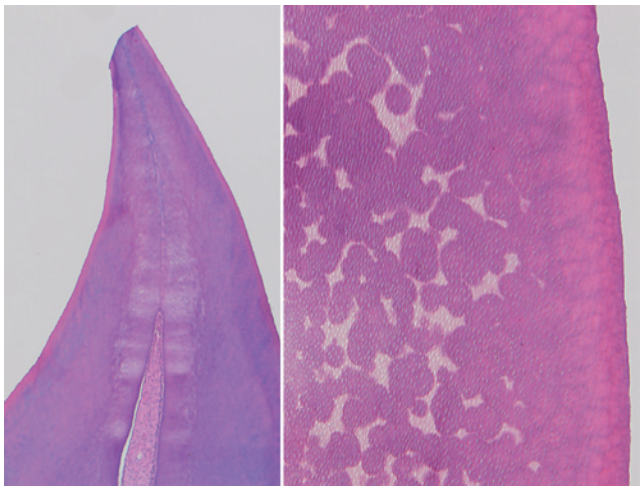


Fig. 2.42 Vitamin D-resistant rickets. A fine pulpal extension into the incisal dentine is just visible on the left. Right, at higher power, there is prominent globular mineralisation of dentine.

Vitamin D-resistant rickets

This term is given to familial hypophosphataemia, a rare X-linked dominant disease causing phosphate loss in the kidneys, and consequent rickets that does not respond to vitamin D. Patients have short legs, wide skull sutures and kyphosis develops during adulthood.

The teeth have abnormally large pulp chambers with fine extensions of the pulp horns to the tips of the cuspal dentine (Fig. 2.42). These are prone to exposure by attrition or fracture and are often invisible radiographically. A periapical granuloma on an apparently normal tooth is a common presentation.

Calcification of dentine is defective. The typical interglobular mineralisation of rickets is seen throughout the dentine.

EXTRINSIC AGENTS AFFECTING TEETH

➔ Summary chart 2.1 p. 26

Drugs

Tetracycline pigmentation

Tetracycline is taken up by calcifying tissues, and the band of tetracycline-stained bone or tooth substance fluoresces bright yellow under ultraviolet light.

The teeth become stained only when tetracycline is given during their development, and it can cross the placenta to stain the developing teeth of the fetus. More frequently, permanent teeth are stained by tetracycline given during infancy. Tetracycline is deposited along the incremental lines of the dentine and, to a lesser extent, of the enamel.

The more prolonged the course of treatment, the broader the band of stain and the deeper the discoloration. The teeth are at first bright yellow but become a dirty brown or grey (Figs 2.43 and 2.44). The stain is permanent, and when the permanent incisors are affected, the dark appearance can only be disguised. When the history is vague, the brownish colour of tetracycline-stained teeth must be distinguished from dentinogenesis imperfecta. In dentinogenesis imperfecta, the teeth are obviously more translucent than normal and, in many cases, chipping of the enamel from the dentine can be seen. In tetracycline-induced defects, the enamel is not abnormally translucent and is firmly attached to



Fig. 2.43 Tetracycline staining. Note the chronological distribution of the dark-brown intrinsic stain.



Fig. 2.44 Tetracycline staining. Now one of the commoner forms of staining, limited to third molar roots from use of minocycline during adolescence.

dentine. In very severe cases, intact teeth may fluoresce under ultraviolet light. Otherwise, the diagnosis can only be confirmed after a tooth has been extracted. In an undecalcified section, the yellow fluorescence of the tetracycline deposited along the incremental lines can be easily seen (Fig. 2.45).

It is no longer necessary to give tetracycline during dental development. There are equally effective alternatives, and it should be avoided from approximately the fourth month to at least the 12th year of childhood, ideally the 16th year. Nevertheless, tetracycline staining is still seen.

Minocycline stain PMID: 23887527

Cytotoxic chemotherapy

Increasing numbers of children are surviving malignant disease, particularly acute leukaemia, as a result of cytotoxic chemotherapy.

Among survivors, teeth that develop during treatment may have short roots, hypoplasia of the crowns and enamel defects. Microscopically, incremental lines may be more prominent, corresponding to growth arrest or delay during the period of chemotherapy. In extreme cases, tooth formation may be aborted so that oligodontia results.

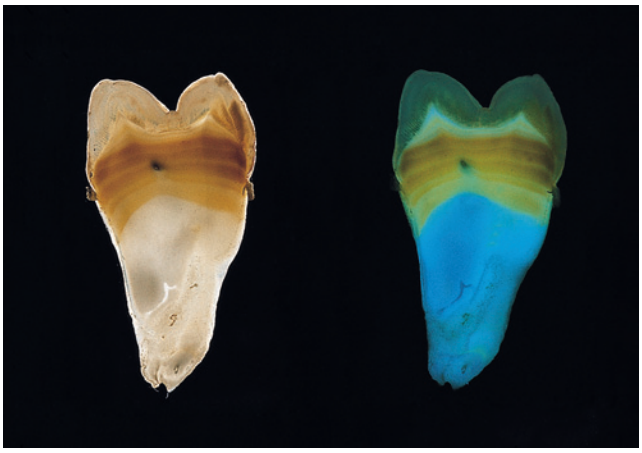


Fig. 2.45 Tetracycline pigmentation. Ground (undecalcified) section (*left*) shows the broad bands of tetracycline deposited along the incremental lines of the dentine; (*right*) same section viewed under ultraviolet light shows fluorescence of the bands of tetracycline.

Box 2.5 Dental fluorosis: distinctive features

- Limited to geographical areas where water-borne fluorides exceed approximately 2 parts per million
- Only those who have lived in a high-fluoride area during dental development show mottling
- The defect is not acquired by older visitors to the area
- Permanent teeth are affected; mottling of deciduous teeth is rare
- Mottled teeth are less susceptible to caries than normal teeth from low-fluoride areas
- A typical effect is spotty paper-white enamel opacities
- Brown extrinsic staining of these patches may be acquired after eruption

Fluorosis → Summary chart 2.1 p. 26

Mottled enamel is the most frequently seen and most reliable sign of excess fluoride in the drinking water. It has distinctive features (Box 2.5). The highest fluoride levels completely disrupt amelogenesis, producing hypoplastic patches. Lower levels inhibit mineralisation and prevent enamel maturation.

Clinical features

Mottling ranges from paper-white matte patches to opaque, brown, pitted and brittle enamel. Clinically, it may be difficult to distinguish fluorotic defects from amelogenesis imperfecta when the degree of exposure to fluoride is unknown (Figs 2.46–2.48).

There is considerable individual variation in the effects of fluorides. A few patients acquire mottling after exposure to relatively low concentrations (Fig. 2.49), while others exposed to higher concentrations appear unaffected. Being a systemic effect, fluorosis is bilateral and usually affects all teeth, though a chronological pattern could result from a limited period of exposure. The perikymata are enhanced and visible clinically in severe cases, producing what appear



Fig. 2.46 Fluoride mottling. In this case, from an area of endemic fluorosis, there is generalised opaque white mottling with patchy enamel hypoplasia. Note the resemblance to the hypomaturation type of amelogenesis imperfecta.



Fig. 2.47 Fluorosis. Moderate effects from an area of endemic fluorosis. Irregular patchy discoloration.



Fig. 2.48 Fluorosis. Severe effects from an area of endemic fluorosis. Closer view showing irregular depressions caused by hypoplasia and white opaque flecks and patches.

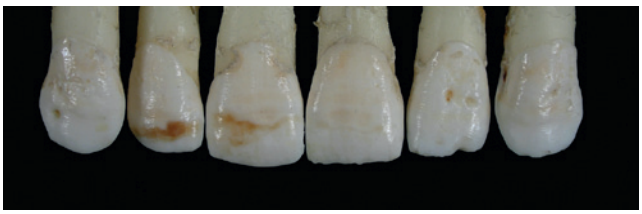


Fig. 2.49 Fluorosis from an area of endemic natural fluorosis in Gloucestershire.

Box 2.6 Grading of mottled enamel

- Very mild. Small paper-white areas involve less than 25% of surface
- Mild. Opaque areas involve as much as 50% of surface
- Moderate. The whole of the enamel surface may be affected with paper-white or brownish areas or both (Fig. 2.47)
- Severe. The enamel is grossly defective, opaque, pitted, stained brown and brittle (Fig. 2.48)

Table 2.1 Effects on enamel of raised fluoride levels

Fluoride concentration	Effects	Clinical appearance
Less than 0.5 ppm	Very mild or mild defects in as many as 6% of patients	Inconspicuous
0.5 to 1.5 ppm	At the upper limit, 22% show very mild defects	
2.5 ppm	Very mild or mild defects in more than 50% Moderate or severe defects in nearly 10%	Noticeable
4.5 ppm	Nearly all patients affected to some degree; 46% have 'moderate' and 18% 'severe' defects	Disfiguring
6.0 ppm and more	All patients affected; 50% severely disfiguring	

to be horizontal lines, which misleadingly suggests chronological hypoplasia.

Changes due to mottling are graded as shown in Box 2.6.

Pathology

Fluoride exerts its effects through inhibition of ameloblasts. At intermediate levels (2–6 ppm), the enamel matrix is normal in structure and quantity. The form of the tooth is unaffected, but there are patches of incomplete calcification beneath the surface layer. These appear as opacities because of high organic and water content that cause light reflection. Where there are high concentrations of fluorides (higher than 6 ppm), the enamel is pitted and brittle, with severe and widespread staining. Deciduous teeth are rarely mottled because excess fluoride is taken up by the maternal skeleton. However, when fluoride levels are excessively high (higher than 8 ppm), as in parts of India, mottling of deciduous teeth may be seen.

With severe mottling of the enamel, other effects of excessive fluoride intake, especially sclerosis of the skeleton, may develop. Radiographically, increased density of the skeleton may be seen in areas where the fluoride content of the water exceeds 8 ppm.

The severity of defects in relation to fluoride concentrations is shown in Table 2.1, and its relationship to caries prevalence in Fig. 2.50.

Mild dental fluorosis is not readily distinguishable from non-fluoride defects, and non-specific defects are more common in areas where the water contains less than 1 ppm of fluoride. Minimal mottling is associated with levels of 1 ppm fluoride in temperate climates and 0.7 ppm in hotter countries.

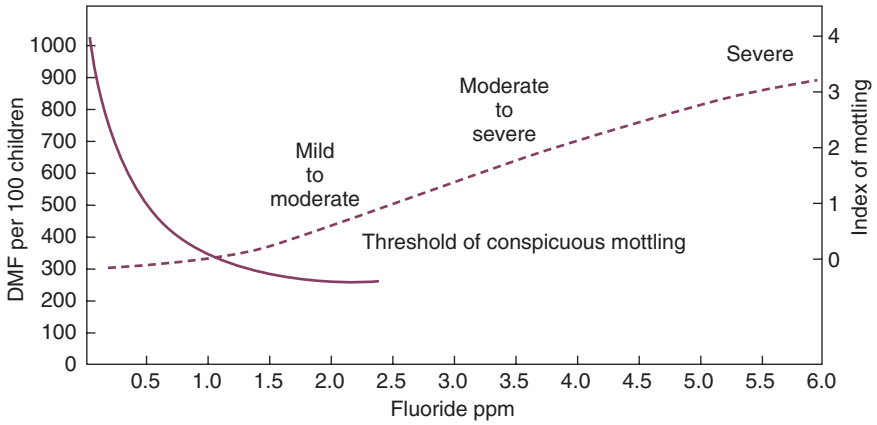


Fig. 2.50 Caries prevalence and mottling. The general relationship between the prevalence of caries (*continuous line*) and the severity of mottling (*broken line*) in persons continuously exposed to various levels of fluoride in the water during dental development. The optimum level of fluoride can be seen to be approximately 1 part per million. Higher concentrations of fluoride cause increasing incidence and severity of mottling without a comparable improvement in resistance to caries. The index of mottling is obtained by giving an arbitrary value for each degree of mottling and relating the numbers of patients with each grade to the total number examined.



Fig. 2.51 A dilacerated upper central incisor. There has been an abrupt change in the direction of root growth after approximately one-third of the root was formed.

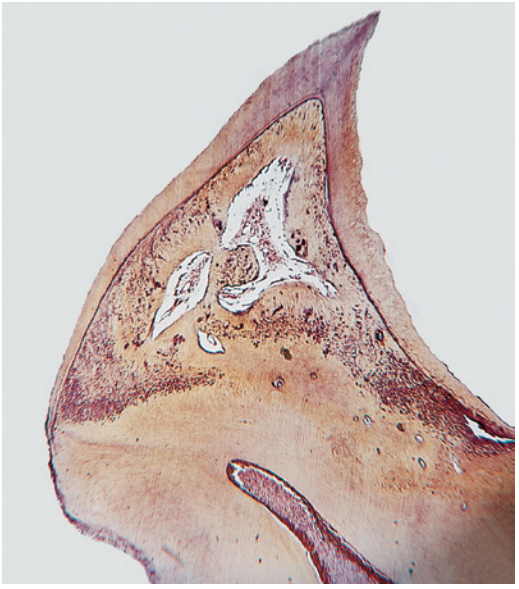


Fig. 2.52 Another dilacerated tooth showing, in addition to the deflected root, a change in enamel contour and disorganised coronal dentine formed after the causative trauma. The junction between dentine formed before and after trauma is clearly seen.

Mild enamel mottling has many causes that cannot usually be distinguished, even by analysis of an extracted or exfoliated tooth.

Treatment of opacities PMID: 26856002

Other acquired developmental anomalies

Dilaceration

Trauma to a developing tooth can cause the root to form at an angle to the normal axis of the tooth – a deformity known as *dilaceration*. The sudden disturbance to odontogenesis may cause the formation of highly irregular dentine at the bend, but the angulated root that develops after trauma is often of normal tubular dentine. The hook-shaped tooth is likely to be difficult to extract (Figs 2.51 and 2.52).

Fetal alcohol syndrome

Maternal alcoholism may cause developmental defects in the fetus. The eyes typically slant laterally, the lower half of the face is elongated and there is learning disability. Dental development may be delayed, and there may be enamel defects, such as mottled opacities in the enamel near the incisal margins, but elsewhere abnormal enamel translucency.

Rhesus incompatibility

Maternal-fetal rhesus blood group incompatibility causes haemolytic disease of the newborn, in which maternal antirhesus antibodies cross the placenta and cause haemolytic anaemia in a fetus with a rhesus-positive blood group. If jaundice is severe, bilirubin can bind to the developing teeth, causing green or grey-yellow discolouration (Fig. 2.53).

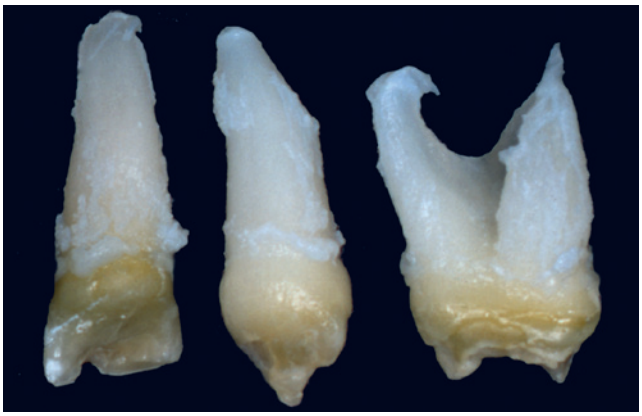


Fig. 2.53 Rhesus incompatibility. Deciduous teeth from a patient who suffered haemolytic anaemia from rhesus incompatibility. There is greenish discolouration of the dentine and enamel formed before birth.

ODONTOMES

Odontomes result from aberrant development of the dental lamina. The most minor examples, although they are not usually called odontomes, are slight malformations, such as an exaggerated cingulum or extra roots or cusps on otherwise normal teeth. All gradations exist between these anomalies and composite odontomes where the dental tissues have developed in a completely irregular and haphazard manner bearing no resemblance to a tooth and occasionally forming a large mass (Ch. 11).

Dens invaginatus is an exaggeration of the process of formation of a cingulum pit. Dentine and enamel-forming tissue invaginate into the pulp to appear radiographically as a tooth-within-a-tooth (*dens in dente,* Fig. 2.54). In the full dens invaginatus, also known as an invaginated or dilated odontome, the invagination extends the whole length of a tooth and sometimes through a widely dilated apex (Fig. 2.55). Often the invagination has incomplete walls allowing the exterior to communicate with the pulp and devitalising it. Alternatively, food debris lodges in the cavity to cause caries which rapidly penetrates the superficially located pulp chamber.

Dens evaginatus is the opposite, an enamel- and dentine-covered spur extending outward from the occlusal surface of a premolar or molar (Fig. 2.56). Fracture exposes the internal pulp horn.

Geminated teeth, meaning double or twinned teeth, are most common in the maxillary incisor region. The pulp chambers may be entirely separate, joined in the middle of the tooth or branched, with the pulp chambers of separated crowns sharing a common root canal. The crowns may be entirely separate or divided only by a shallow groove. The roots may be single or double. These defects are commoner in the deciduous dentition. In the past, effort has been expended trying to decide whether such teeth arise by fusion of two tooth germs or partial splitting of a single germ. This distinction is pointless, and it seems likely that the condition is genetic; it is often bilateral and is rarely seen in excessive crowding.

These malformed teeth usually need to be removed before they obstruct the eruption of other teeth or become infected, or for cosmetic reasons.

Enamel pearls are uncommon, minor abnormalities that are formed on otherwise normal teeth by ameloblasts that differentiate below the amelocemental junction. The pearls are usually round, a few millimetres in diameter and often

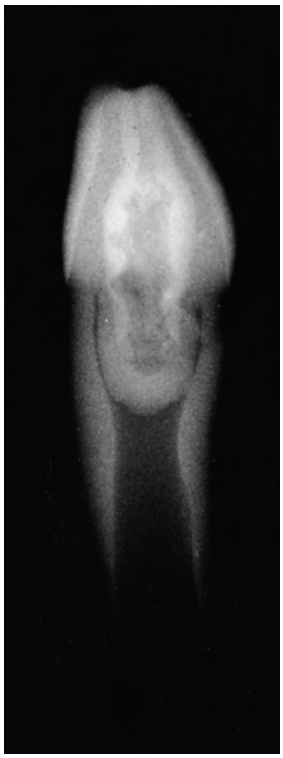


Fig. 2.54 Dens in dente or mild invaginated odontome. In this radiograph, the enamel-lined invagination and its communication with the exterior at the incisal tip are clearly seen. The pulp is compressed to the periphery.



Fig. 2.55 A dilated and invaginated odontome in a lateral incisor, sectioned vertically. The central cavity communicates with the exterior through an invagination in the cusp tip.



Fig. 2.56 Dens evaginatus from a lower premolar, occlusal surface inset.



Fig. 2.57 **Enamel pearl.** There is a small mass of enamel at the root bifurcation.



Fig. 2.58 Enamel pearl associated with a spur of enamel joining the crown to the pearl.

Box 2.7 **Normal teething**

One-third of infants have no signs or symptoms. Many only have a few.

- Effects are limited to a few days each side of the day of eruption
- Increased biting and rubbing the gingiva
- Reflex salivation and drooling
- Irritability and sleep disturbance
- Rubbing of face and ears
- Facial reddening of the cheek
- Decreased appetite
- Mild temperature increase

form at the bifurcation of upper permanent molars (Figs 2.57 and 2.58).

Enamel pearls may consist of only a nodule of enamel attached to the dentine, or may have a core of dentine containing a horn of the pulp. They may cause a stagnation area at the gingival margin but, if they contain pulp, this will be exposed when the pearl is removed. The enamel and dentine are normal histologically.

DISORDERS OF ERUPTION

Normal eruption

Eighteenth-century parish registers are replete with the names of infants who died as a result of teething. Although this is now considered impossible, other myths about tooth eruption abound.

Teething coincides with a period of naturally low resistance to infection and declining maternal passive immunity during which viral infections are common. Eruption is associated with a very slight rise in temperature (not a fever), mild discomfort locally, reflex salivation causing drooling and, sometimes, reddening of cheeks. Systemic symptoms during teething should therefore be investigated because, if significant, they are more likely to be caused by primary herpetic gingivostomatitis or other treatable infection. In many infants teething passes unnoticed (Box 2.7). The signs and symptoms are not specific and are also seen in those not teething, in whom they pass unremarked.

Fusion of the enamel epithelium with the oral epithelium allows eruption without bleeding, but the urge to chew during teething is strong, and trauma to the mucosa may cause haemorrhage over an erupting tooth before it reaches the surface ('eruption haematoma', Fig. 10.23).

Very occasionally eruption of permanent molars is associated with painless loss of a small sequestrum. Bone lying in the concavity of the crown can be resorbed around the periphery while the cusps erupt, cutting off its blood supply from adjacent tissues ('eruption sequestrum'). Lower first permanent molars are the most frequently affected teeth.

Symptoms of teething PMID 10742315

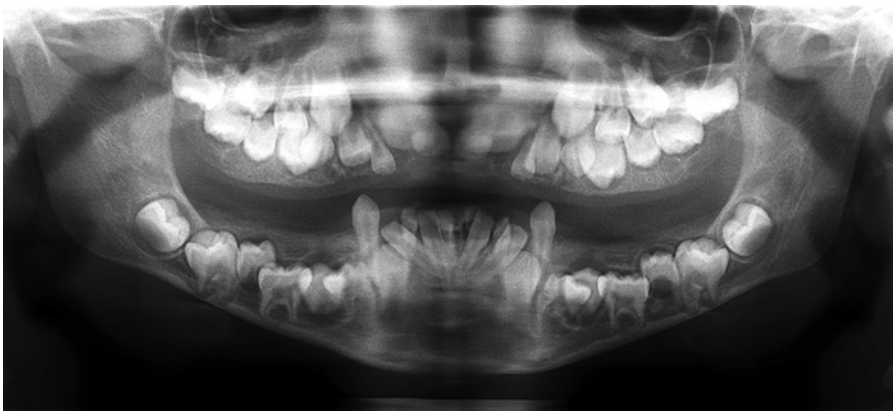


Fig. 2.59 Primary failure of eruption. A few teeth have erupted anteriorly, but after the last erupted tooth standing, none have erupted.

Natal teeth

Teeth present at birth or shortly afterward are called *natal teeth*. Almost always these are normal deciduous lower incisors that erupt prematurely. Occasionally they may be supernumerary teeth, though deciding this can be difficult as radiographs are difficult to take at such a young age. Removal may be required to aid feeding or when inadequate root development risks their displacement and inhalation, but they are best retained.

Bohn's nodules may be mistaken for erupting teeth in neonates.

Natal teeth are seen in a number of rare developmental disorders, pachyonychia congenita, Ellis-van Creveld and Hallermann-Streiff syndromes.

Delayed eruption

Eruption of deciduous teeth starts at approximately 6 months, usually with the appearance of the lower incisors, and is complete by approximately 2 years, earlier in females and with considerable individual variation in timing. Mass failure of eruption is very rare despite the biological complexity of the process. More often eruption delay has local causes and affects one or a few teeth.

Failure of a single tooth or adjacent teeth to appear in the mouth within a few months of the contralateral equivalent should trigger radiographic assessment to check for its presence and location. However, delayed appearance of the deciduous dentition in the absence of a cause does not warrant concern until it is delayed for 1 year provided no mechanical cause is evident, as eruption times are so variable.

In generalised delay caused by systemic illness, for instance in preterm infants, recovery normally allows eruption to proceed and after a few years eruption catches up with the normal timetable. Systemic diseases that cause delayed eruption are all rare. Eruption is complex, and many diseases can interfere with it. Both chemotherapy and radiotherapy arrest or interrupt eruption as well as tooth formation.

Single tooth failure of eruption is almost always due to a mechanical obstruction or ankylosis.

Primary eruption failure is a rare condition. Usually some teeth erupt, but then all teeth distally in the quadrant, sometimes all, remain unerupted and may eventually ankylose (Fig. 2.59). Half of cases are familial, and some are associated with mutation of the parathyroid hormone receptor gene. A common mild presentation is failure of eruption of only permanent molars, and the first permanent molars are almost always involved. There may be bilateral involvement, a Class 3 skeletal pattern and oligodontia associated. This condition does not cause delayed eruption of single teeth. Teeth in primary eruption failure do not respond to orthodontic traction, and treatment usually requires extraction. Restoration is then difficult due to lack of alveolar bone growth.

Causes of delayed eruption are shown in Box 2.8.

Primary eruption failure PMID: 17482073

Changes affecting buried teeth

Teeth may occasionally remain unerupted in the jaws for many years without complications, or may undergo varying degrees of hypercementosis or resorption (Ch. 6). Alternatively, dentigerous cysts may develop (see Ch. 10), as often happens in cleidocranial dysplasia.

Box 2.8 Causes of delayed eruption of permanent teeth

Localised

- Impaction, usually last teeth in any series
- Insufficient space in the arch, crowding, supernumerary teeth
- Retention of a deciduous predecessor, ankylosis
- Premature loss of a deciduous predecessor, before half of the successor root is formed
- Malposition
- Local pathological process
 - Odontogenic cysts and tumours
 - Cherubism
- Defects of the teeth
 - Dilaceration
 - Connate teeth
 - Turner teeth
 - Regional odontodysplasia
 - Segmental odontomaxillary dysplasia

Generalised

- Delayed development
 - Malnutrition
 - Down's syndrome (Ch. 39)
 - Hypothyroidism (cretinism) (Ch. 36)
 - Hypoparathyroidism and pseudohypoparathyroidism
 - Hypopituitarism
- Metabolic disease with delayed growth
 - Rickets (Ch. 13)
 - Infants with premature birth
 - Human immunodeficiency virus infection in infancy (Ch. 29)
- Increased resistance of overlying mucosa
 - Scarring
 - Hereditary gingival fibromatosis (Ch. 7)
 - Drug-induced gingival overgrowth (Ch. 7)
- Iatrogenic
 - Chemotherapy for malignant neoplasms
 - Radiotherapy to the jaws
- Increased resistance of bone or reduced bone turnover
 - Osteopetrosis
 - Gaucher's disease
- Complete or near complete failure of eruption
 - Cleidocranial dysplasia (Ch. 13)
 - Idiopathic or primary eruption failure

Disorders of development 3

Important developmental defects of the jaws are summarised in Box 3.1, and some are discussed more fully in other chapters.

CLEFTS OF LIP OR PALATE

Clefts of the palate alone and those of the lip, with or without cleft palate, are genetically distinct conditions. The embryology of the lower face and mechanisms of closure of the palatal shelves and fusion of the soft tissue processes to form the upper lip are very complex. Until around 6 weeks of development, the mouth and future nasal cavity are one. Then fusion of the median nasal process and maxillary processes of the first branchial arch forms the midline alveolar ridge and anterior palate, or primary palate. By the end of week 9, the secondary palate has formed by growth of the palatal shelves, their rotation and fusion. Formation of a complete palate therefore requires growth and migration of tissues, breakdown of epithelium to allow fusion and growth of the mandible to allow the tongue to drop out of the way. The process takes slightly longer in females, and the longer period of development makes them more prone to palatal clefts than males. Many genes are involved, and there is a relatively long period during which an environmental insult could interfere with the process. Approximately one in 700 babies have clefts of lip and/or palate. Mechanisms are summarised in Figs 3.1 and 3.2.

The sites of clefts vary because the lip and anterior palate (the primary palate) develop independently and before the hard and soft palates (the secondary palate). Isolated cleft lip is therefore the result of an early developmental disorder, whereas isolated cleft palate results from influences acting later, after the primary palate has closed. By contrast, a prolonged disorder of development can prevent both primary and secondary palates from closing and leaves a severe combined defect (Figs 3.3 and 3.4).

Clefts of lip and palate form because of failure of growth and migration of mesenchyme to form the alveolus and lip, not because an embryological line of fusion fails to close. In contrast, cleft palate develops because of failure to close the cleft during development.

The main types of cleft are summarised in Box 3.2. A complete cleft of the lip is one that extends into the nose, completely separating the lip into two portions. Incomplete clefts are limited to lip or lip and alveolus, and there is some continuity between the segments to stabilise the tissues.

Cleft lip and cleft palate

Cleft lip (with or without a palatal cleft) is a single condition that presents with varying degrees of severity. It is the most common craniofacial anomaly and affects approximately 1 per 1000 live births, roughly half of whom have a cleft lip alone and half of whom have cleft lip with a cleft palate. Twice as many males as females are affected, and the right side is twice as frequently involved.

There is a strong genetic background to cleft lip and palate, but the aetiology is complex. Either dominant or recessive inheritance can be found in familial cases, whereas others appear multifactorial. The risk of having such defects is considerably greater if one, and particularly if both, of the parents are affected or if the cleft is more severe. There are many candidate genes affecting different stages of palate development. Hedgehog pathway and PTCH gene variants affect growth and patterning, and TGF beta is involved in fusion. Many other genes have been implicated. IRF6 (interferon regulatory factor 6), FGFR2 (fibroblast growth factor receptor 2), MSX1 (Msh homeobox1), fibroblast growth

Box 3.1 Developmental defects of the jaws, mouth and face

Defects of the jaws

- Clefts of the palate and/or lip
- Cleidocranial dysplasia (Ch. 13)
- Cherubism (Ch. 13)
- Basal cell naevus syndrome (Ch. 10)
- Gardner's syndrome (Ch. 12)
- Osteogenesis imperfecta (Ch. 13)
- Craniofacial anomalies
- Hereditary prognathism

Defects of the soft tissues

- Ankyloglossia
- Cowden's syndrome
- Ehlers-Danlos syndrome (Ch. 14)
- Branchial and thyroglossal cysts (Ch. 10)
- Lingual thyroid (Ch. 36)
- White sponge naevus (Ch. 18)
- Some pigmented lesions (Ch. 26)

Defects of the teeth (Ch. 2)

Box 3.2 Clefts of lip and/or palate

Cleft lip

- Unilateral (usually on the left side), with or without an anterior alveolar ridge cleft
- Bilateral, with or without alveolar ridge clefts, complete or incomplete

Palatal clefts

- Bifid uvula
- Soft palate only
- Both hard and soft palate

Combined lip and palatal defects

- Unilateral, complete or incomplete
- Cleft palate with bilateral cleft lip, complete or incomplete

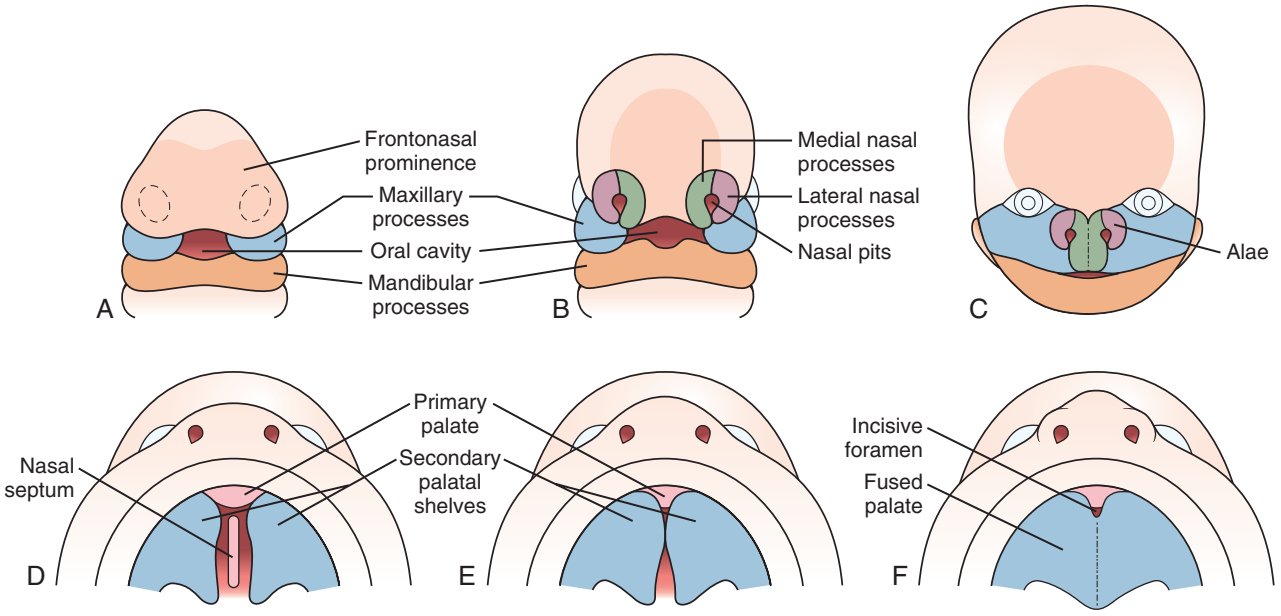


Fig. 3.1 Development of the lip and palate. Schematic diagrams of the development of the lip and palate in humans. (A) The developing frontonasal prominence, paired maxillary processes and paired mandibular processes surround the primitive oral cavity by the fourth week of embryonic development. (B) By the fifth week, the nasal pits have formed, which leads to formation of the paired medial and lateral nasal processes. (C) The medial nasal processes have merged with the maxillary processes to form the upper lip and primary palate by the end of the sixth week. The lateral nasal processes form the nasal alae. Similarly, the mandibular processes fuse to form the lower jaw. (D) During the sixth week of embryogenesis, the secondary palate develops in the form of bilateral outgrowths from the maxillary processes, which grow vertically down the side of the tongue. (E) Subsequently, the palatal shelves elevate to a horizontal position above the tongue, contact one another and commence fusion. (F) Fusion of the palatal shelves ultimately divides the oronasal space into separate oral and nasal cavities.
(From Dixon, M.J., Marazita, M.L., Beaty, T.H., et al. 2011. Cleft lip and palate: understanding genetic and environmental influences. Nat Rev Genet. 12(3), pp. 167-178.)

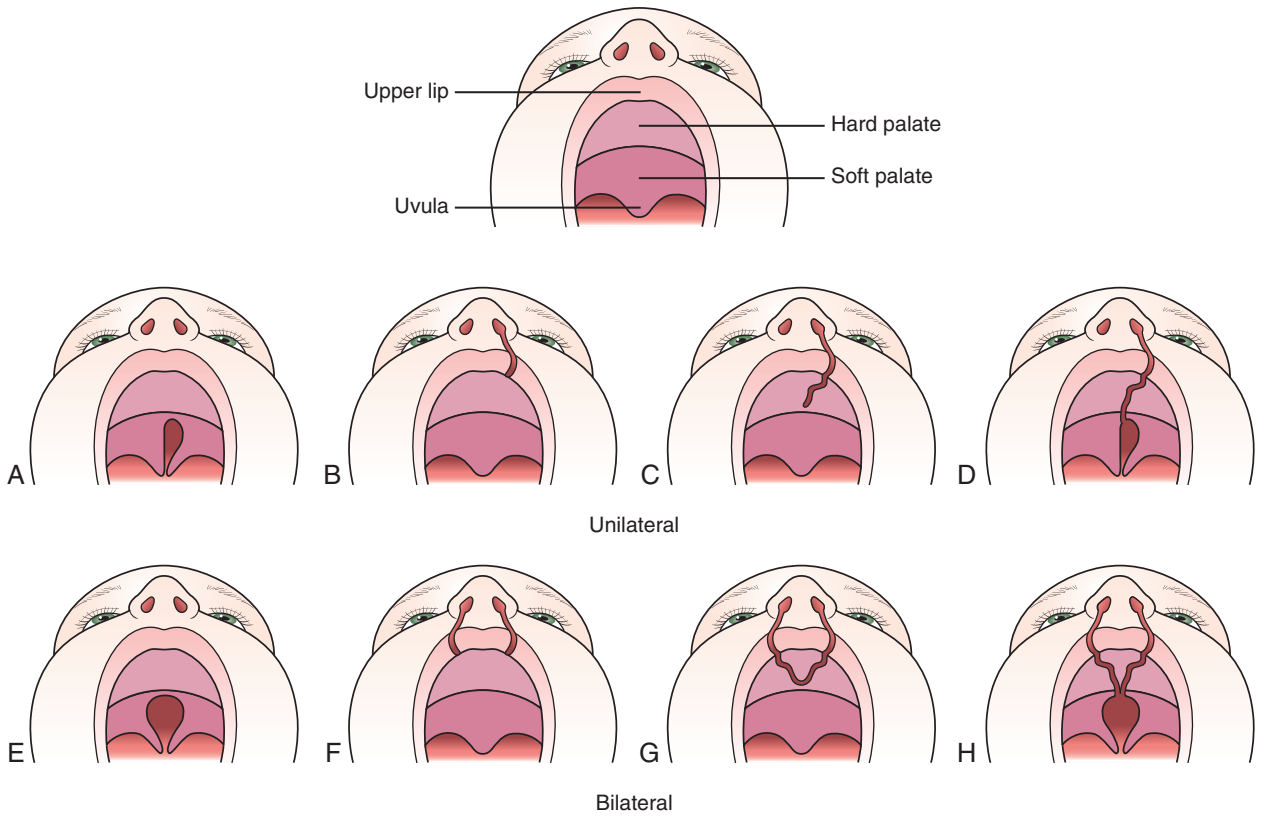


Fig. 3.2 Cleft lip and palate types. A set of illustrative drawings of cleft lip and palate types. A and E show unilateral and bilateral clefts of the soft palate; B, C and D show degrees of unilateral cleft lip and palate; and F, G and H show degrees of bilateral cleft lip and palate.
(From Dixon, M.J., Marazita M.L., Beaty, T.H., et al. 2011. Cleft lip and palate: understanding genetic and environmental influences. Nat Rev Genet. 12(3), pp. 167-178.)



Fig. 3.3 Cleft palate. A broad midline defect is present. *(By kind permission of Mrs E Horrocks.)*



Fig. 3.4 Cleft lip and palate. Complete unilateral cleft of palate, alveolar bone and lip joining the oral and nasal cavities. *(By kind permission of Mrs E Horrocks.)*

Box 3.3 Management of clefts: important considerations

- Psychological support for the family and later the patient
- Provision for feeding in infancy when palatal clefts are severe
- Prevention of movement of the two halves of the maxilla or premaxilla pending surgery
- Measures to counteract speech defects
- Cosmetic repair of cleft lips
- Later closure of palate
- Monitoring for hearing loss
- Speech and language therapy
- Aggressive dental prevention regime
- Restoration of anterior teeth
- Genetic counselling if syndromic

factors (FGF1 and FGF8) and BMP4 (bone morphogenetic protein 4) are the most likely.

Environmental causes are also recognised and include smoking and alcohol, phenytoin and retinoids and other drugs. These environmental causes usually cause clefts combined with other developmental defects.

Review PMCID: PMC3086810

Management

The birth of a baby with a cleft lip triggers very early involvement of a multidisciplinary team. Important considerations are summarised in Box 3.3. Immediate considerations are psychological support for the family, both for the initial shock and during many years of treatment to follow. It is important to establish feeding as soon as possible. Cleft lip alone causes few problems, but a cleft palate prevents suckling, and either a feeding plate to close the defect or specially designed feeding bottles may be required.

Cleft lip is closed surgically, eliminating the cleft, repairing the continuity of the lip muscle and recontouring the philtrum and nasal aperture. Early surgery has best results with least subsequent scarring and distortion, so repair is usually performed at approximately 3 months, but earlier in some centres.

The palatal cleft is treated initially by an obturator plate that must be replaced regularly as the child grows. Surgery is performed between 9 and 12 months of age, and a bone graft may be required for wide defects. Palatal surgery leads to scarring that inhibits maxillary growth and contributes to the class III appearance of the face in later life. Re-operation may be necessary to lessen the deformity (Fig. 3.5).

Between the ages of 1 and 5 years, attention needs to be paid to hearing, for which ear grommets may be necessary to prevent otitis media and hearing loss. The distorted soft palate musculature fails to open the pharyngeal end of the Eustachian tube, predisposing to glue ear and infection. Poor hearing may interfere with development of speech, already compromised by the inability of the soft palate to effectively seal off the nose when plosive sounds (such as 'p' or 'b') are made. Speech therapy and sometimes soft palate surgery



Fig. 3.5 Collapsed maxilla resulting from poorly timed surgical repair of cleft palate. Scarring and growth disturbance produce a distorted narrow maxilla. *(By kind permission of Mrs E Horrocks.)*

may be undertaken between the ages of 3 and 8 for these reasons. At approximately the age of 8 years, orthodontic treatment may start depending on need, and this and further possible surgery to reconstruct the anterior alveolus or palatal cleft may continue for several years. Thereafter, up to late teenage years, final measures are to improve appearance include excision of scars, rhinoplasty and orthognathic surgery.

More recently, observation of untreated clefts has shown that the growth potential of these tissues is virtually normal. In some centres, therefore, a soft palate cleft is repaired early, but hard palate repair is delayed until 8 or 9 years after temporary closure with an obturator. The results are good facial growth and occlusion, but speech may be impaired to some degree.

The forward rotation of the premaxilla in bilateral clefts can be managed by repositioning of this segment with bilateral bone grafts. Severe maxillary deficiency may be managed by Le Fort I internal distraction to remedy malocclusion and speech defects.

Despite several large clinical trials, controversies remain about the timing of these operations and the optimum approach.

Treatment review PMCID: PMC2884751

Dental defects

However effective the treatment, patients with clefts tend to have poor oral hygiene gingivitis and dental caries necessitating regular preventive care.

Teeth in the region of the defect are typically absent, malformed or have hypoplastic enamel. Development and eruption are delayed on the cleft side. Severe clefts are associated with absent teeth. Milder defects are peg-shaped lateral incisors and, sometimes, development of a diminutive lateral incisor on both sides of the cleft. Both deciduous and permanent dentitions are affected.

Isolated cleft palate

Clefts of the hard palate alone arise when the primary palate and lip form, but the palatal shelves fail to fuse posteriorly. The cleft is wider more posteriorly and narrow anteriorly because the shelves fuse from front to back starting at the incisive foramen.

Isolated cleft palate affects approximately 1 in 2000 births and is approximately twice as common in females. Only occasional cases are inherited, but there is a risk of approximately 2% that a second child will be affected.

Extensive review PMCID: PMC4771933

Submucous cleft palate

Submucous clefts are clefts of the bone or muscle covered by intact mucosa, and they are thus usually visible only as a translucent area along the midline of the soft palate. They are present in approximately 1 in 1200 births but are frequently missed. A bifid uvula is a frequent sign of a submucous cleft.

On palpation the bony cleft and a notched posterior nasal spine may be felt, and the diagnosis can be confirmed by imaging. Submucous clefts cause problems through the distortion of the attachment of the muscles of the soft palate. The chief effects are slowness in feeding and nasal regurgitation. Middle ear infections and speech defects result from the defective muscle attachments and Eustachian tube function, as in overt clefts. Some symptoms are present in 90% of cases.

Operation to repair the muscle attachments is usually delayed for about 2½ years to enable the speech and degree of the defect to be assessed.

Case bifid uvula PMID: 26076543

Management

Isolated cleft palate may be missed at birth but almost immediately comes to light by causing feeding problems. Isolated cleft palate is treated in the same way as those associated with cleft lip.

Syndromic cleft lip and palate

Approximately 30% of all cases of cleft lip and palate and 50% of cases of cleft palate arise as part of a recognised syndrome. The most common of these is Down's syndrome, in which cleft lip or palate is present in approximately 1 in 200 patients (Ch. 39). Other syndromes with clefts are single gene defects, and the genes involved are often the same as those implicated in non-syndromic clefts. Different mutations, polymorphisms, variable penetrance or gene control probably account for the different presentations.

Note that a cleft can be the most prominent sign of a syndrome, and also that these syndromes are often associated with other features that affect dental treatment, such as cardiac defects, learning difficulties and dental anomalies.

Van der Woude syndrome comprises cleft lip and cleft primary and secondary palate (usually a rare combination), lower lip pits, oligodontia, a high arched palate, ankyloglossia and other features. The syndrome is inherited in an autosomal dominant pattern caused by one of several genes, but usually *IRF6*. The lip pits are characteristic, usually one each side of the midline and occasionally at the commissures or in the midline of the upper lip (Fig. 3.6). The pits extend several millimetres deep into the lip and may communicate with labial glands, but are not dilated minor gland ducts, rather a developmental groove between growth centres in the embryonic lip. Lip pits may also be seen in other syndromes but less frequently.

OTHER FACIAL CLEFTS

There are more extensive clefts that can develop along the lines of fusion of the maxillary and frontonasal processes,



Fig. 3.6 van der Woude syndrome. Cleft lip and lower lip pits. *(From Hartzell L.D., Kilpatrick L.A., 2014. Diagnosis and management of patients with clefts: a comprehensive and interdisciplinary approach. Otolaryngol Clin North Am, 47, pp. 821-852.)*



Fig. 3.7 Lateral facial cleft, a severe lateral cleft and severe bilateral cleft lip and palate. *(From Journal of Cranio-Maxillo-Facial Surgery 42 (2014) 1985e1989 42:1985-9.)*

often involving the eye and sometimes the cranium (Fig. 3.7). These are associated with severe distortion of the face, often with major tissue deficiency. Such facial clefts are usually continuous with a cleft lip and palate at their inferior end. Surgical correction of the defects is extremely difficult.

STAFNE'S IDIOPATHIC BONE CAVITY

This is a relatively common developmental anomaly caused by a lobe of the submandibular gland indenting the lingual aspect of the mandible, below the level of the inferior dental nerve canal. The cortex is invaginated into the medullary space. In a panoramic or oblique lateral radiograph the concavity appears to be a circumscribed cyst in the mandible, surrounded by a layer of cortical bone.



Fig. 3.8 Stafne idiopathic bone cavity.

Very occasionally one of these cavities arises in the anterior mandible, caused by inclusion of part of the sublingual gland, or ectopic salivary gland.

This condition should be diagnosed radiographically (Fig. 3.8). The cavity has a smooth rounded outline and thick even cortication and does not enlarge. Almost all are unilateral, and most patients are male. Although developmental, it appears that the cavity develops slowly in the second or third decades. Cone beam or other tomographic techniques can confirm that the mandible is indented, rather than containing a cavity. Once diagnosed, no treatment is required, and the change appears to be of no significance.

HEREDITARY PROGNATHISM

The extreme genetic form is often called 'Habsburg jaw'* and is probably a single gene disorder inherited as an autosomal dominant. Although this severe inherited form is still occasionally found, most families with a protruding mandible may simply be at one end of the spectrum of normal variation, and result from polygenic inheritance. Marked prognathism can also be seen as an acquired condition in acromegaly.

ANKYLOGLOSSIA

Ankyloglossia, or tongue tie, is caused by tethering of the tongue tip to the floor of mouth, lingual alveolar mucosa or gingiva by a short lingual fraenum (Fig. 3.9). In severe cases a broad thick fraenum effectively fuses the anterior tongue

*Hereditary prognathism has been associated with the Habsburg dynasty. Originally a Swiss family, the Habsburgs ruled many European countries between the 11th and 18th centuries. The trait persisted for generations through interbreeding between European royal families, particularly in the Spanish branch. However, recent evaluation of portraits suggests that the family's striking appearance was caused in part by additional hypoplasia of the maxilla, accentuating the appearance. (Peacock, Z.S., Klein, K.P., and Mulliken, J.B., et al. 2014. The Habsburg jaw–re-examined. *Am J Med Genet.* 164A, pp. 2263-2269. [PubMed: 24942320])

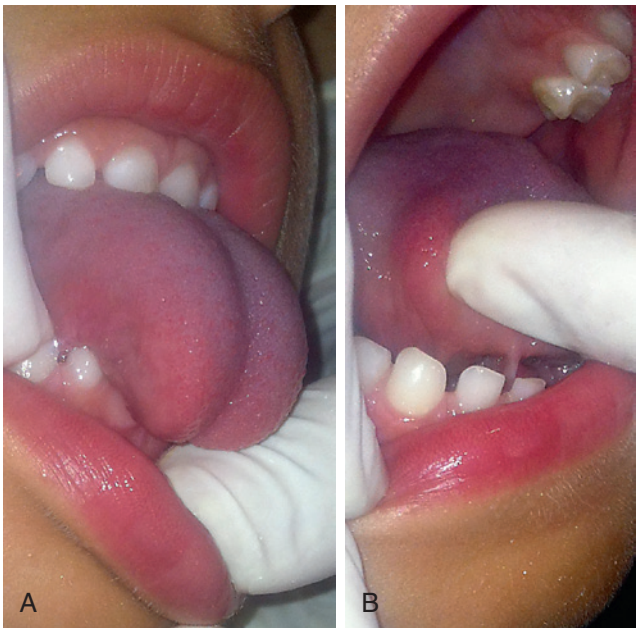


Fig. 3.9 Ankyloglossia. On the left the patient has been asked to protrude the tongue, but the tip is tethered to the lingual gingiva and the dorsum furrows along the midline. The tongue has to be displaced to see the tight lingual fraenum (*right*).

to the floor of mouth. The cause is unclear but has been associated with several genes known to cause cleft palate and clefting syndromes. However, most cases are solitary abnormalities and often have a family history suggesting an autosomal dominant inheritance. Nearly half of affected individuals will have an affected first-degree relative. When there is no family history, males are usually affected. The incidence is approximately 3%.

Reduced lingual mobility can affect feeding in the neonatal period and development of an adult pattern swallow, disturbing the soft tissue guidance for tooth position. A high frenal attachment may cause a midline diastema. Speech can be affected when the tongue tip cannot contact the upper incisors. However, patients develop compensatory speech and swallowing mechanisms, and the condition often regresses slightly during early childhood, so there may be no significant consequences. However, the inability to sweep food debris from the mouth, protrude the tongue or eat ice cream from a cone may drive adults to seek treatment.

Routine surgical treatment is therefore controversial. The fraenum is easily divided and, if there are feeding difficulties, this is appropriate and much more easily performed shortly after birth than in an older child or adult. It is also likely to be most effective before speech and swallowing are established. In general, if a fraenum is attached to the ridge rather than the floor of mouth or within 10 mm of the tongue tip and is not elastic, it is likely to cause problems.

Not all functional tongue tie is associated with an obvious fraenum. The so-called *posterior tongue tie* is a fibrous band below the mucosa tethering the centre of the tongue. It is posterior to the usual site, but still in the anterior tongue, and best thought of as a *deep tongue tie*. The band may only be palpable or noticed because the tongue dimples centrally on movement or will not protrude. Posterior ties also cause feeding problems.



Fig. 3.10 Cowden's syndrome. Multiple nodules and papillomatous nodules on labial mucosa and alveolar ridge. *(From Flores, I.L., Romo, S.A., Tejeda Nava, F.J., et al. 2014. Oral presentation of 10 patients with Cowden syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol, 117(4), pp. e301-e310.)*

Ankyloglossia can develop in adults as a result of scarring diseases, typically severe forms of epidermolysis bullosa, in which the sulci become gradually obliterated by fibrosis.

Feeding problems PMID: 12415069

Diagnosis and treatment PMID:15839394

COWDEN'S SYNDROME

Multiple hamartoma or Cowden's syndrome* is a genetically diverse condition in which patients have mucosal polyps in the gastrointestinal tract, multiple skin and oral nodules and a high risk of developing malignant neoplasms. Mutations are classically in the PTEN gene, although many variants associated with other genes exist.

Inheritance is usually autosomal dominant and skin, and mucosal lesions develop in the second decade. Skin lesions are more obvious, multiple nodules 1 or 2 mm in diameter around the nose and mouth particularly (Fig. 3.10). Histologically the nodules can be found to be caused by a variety of hamartomas including trichilemmomas and neuromas. Multiple oral nodules develop on the dorsum of the tongue, gingiva and buccal mucosa. The appearance is often referred to as *papillomatosis* because of its shape, but viral papillomas are not a feature. All these nodules are benign.

Diagnosis is largely clinical because the oral lesions appear like fibroepithelial polyps and have no specific features. Suspected cases need urgent investigation because the risk of breast and thyroid carcinomas in later life is so high.

Web URL 3.1 Review: http://emedicine.medscape.com/article/1093383-overview

Web URL 3.2 Online risk assessor: http://www.lerner.ccf.org/gmi/ccscore/

OTHER CRANIOFACIAL MALFORMATIONS

There are many rare syndromes and diseases with characteristic craniofacial abnormalities. Key features are shown in Table 3.1. The craniosynostoses are caused by early fusion of sutures, distorting the shape of the skull while it grows.

*Cowden's syndrome is one of the few syndromes named after the patient, rather than the person who first described it.